Access DB# 64950

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: Iesha Fields Examiner #: 77985 Date: 4-29-02
Art Unit: 1645 Phone Number 30[redacted]1208 Serial Number: 09/674935
Mail Box and Bldg/Room Location: [redacted] Results Format Preferred (circle): PAPER DISK E-MAIL
8E12 8A13

If more than one search is submitted, please prioritize searches in order of need. mej

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Point of Contact:
Mona Smith
Technical Information Specialist
CM1 6A01
Tel: 308-3278

Title of Invention: Vaccine

Inventors (please provide full names): Timothy Hirst et al

Earliest Priority Filing Date: 5-10-99 Before May 21, 1999

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Please search claims 1-35
Invention is a bacterial toxin (EtxB, CtxB or VtxB) vaccine.
EtxB = E. coli heat-liable enterotoxin
CtxB = Cholera toxin
VtxB = E. coli verotoxin.
GM1 = GM1-ganglioside
Please also include Inventor(s) patents and publications.

Thanks.

DATE RECD APR 22 2002

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STAFF USE ONLY	Type of Search		Vendors and cost where applicable	
Searcher: M. SMITH	NA Sequence (#)		STN	
Searcher Phone #:	AA Sequence (#)		Dialog	
Searcher Location:	Structure (#)		Questel/Orbit	
Date Searcher Picked Up:	Bibliographic	X	Dr.Link	
Date Completed: 5/6/02	Litigation		Lexis/Nexis	
Searcher Prep & Review Time: 50	Fulltext		Sequence Systems	
Clerical Prep Time:	Patent Family		WWW/Internet	
Online Time: 60	Other		Other (specify)	

PTO-1590 (8-01)

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FILE LAST UPDATED: 23 Apr 2002  (20020423/ED)

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information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d stat que
L1          112 SEA FILE=HCAPLUS "HIRST T"/AU OR ("HIRST T R"/AU OR "HIRST
                TIM"/AU OR "HIRST TIM R"/AU OR "HIRST TIMOTHY R"/AU OR "HIRST
                TIMOTHY RAYMOND"/AU OR "HIRST TIMOTHY RAYMOND"/IN OR "HIRST
                TOMOTHY R"/AU)
L2          133 SEA FILE=HCAPLUS "WILLIAMS N"/AU OR ("WILLIAMS N A"/AU OR
                "WILLIAMS N A"/IN)
L3          165 SEA FILE=HCAPLUS MORGAN/AU OR "MORGAN A"/AU OR ("MORGAN
                ANDREW"/AU OR "MORGAN ANDREW"/IN)
L4          414 SEA FILE=HCAPLUS ("WILSON A"/AU OR "WILSON A"/IN) OR ("WILSON
                A D"/AU OR "WILSON A DOUGLAS"/AU) OR ("WILSON ANDREW"/AU OR
                "WILSON ANDREW"/IN)
L5           22 SEA FILE=HCAPLUS "BIRD L"/AU OR "BIRD LUCY"/AU
L7          839 SEA FILE=HCAPLUS L1 OR L2 OR L3 OR L4 OR L5
L8           28 SEA FILE=HCAPLUS L7 AND (VACCIN? OR BACTERIAL(W)TOXIN?)


=> d ibib abs hitrn l8 1-28

L8   ANSWER 1 OF 28  HCAPLUS  COPYRIGHT 2002 ACS
ACCESSION NUMBER:         2001:798749  HCAPLUS
DOCUMENT NUMBER:          135:339267
TITLE:                    Therapeutic agents
INVENTOR(S):              Williams, Neil Andrew; Hirst, Timothy Raymond
                          ; Nashar, Toufic Osman
PATENT ASSIGNEE(S):       UK
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SOURCE: U.S. Pat. Appl. Publ., 53 pp., Cont.-in-part of U.S. 6,287,563.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2001036917	A1	20011101	US 2001-867914	20010530
PRIORITY APPLN. INFO.:			GB 1995-13733 A	19950705
			US 1997-999458 A2	19971229

AB A method of treating diabetes in a mammalian subject by administering an agent capable of modulating a ganglioside GM-1 (GM-1) assocd. activity in an amt. effect to treat the disease; wherein agent is selected from the group consisting of cholera toxin (Ctx), enterotoxins (Etx), the B subunit of Ctx and the B subunit of Etx, mutants and derivs. thereof. along with co-administration of antigens which are not so linked to form a single active agent.

L8 ANSWER 2 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:309960 HCAPLUS
DOCUMENT NUMBER: 135:75460
TITLE: Escherichia coli heat-labile enterotoxin B subunit is a more potent mucosal adjuvant than its closely related homologue, the B subunit of cholera toxin
AUTHOR(S): Millar, Douglas G.; **Hirst, Timothy R.**; Snider, Denis P.
CORPORATE SOURCE: Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, L8N 3Z5, Can.
SOURCE: Infection and Immunity (2001), 69(5), 3476-3482
CODEN: INFIBR; ISSN: 0019-9567
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although cholera toxin (Ctx) and Escherichia coli heat-labile enterotoxin (Etx) are known to be potent mucosal adjuvants, it remains controversial whether the adjuvanticity of the holotoxins extends to their nontoxic, receptor-binding B subunits. Here, we have systematically evaluated the comparative adjuvant properties of highly purified recombinant EtxB and CtxB. EtxB was found to be a more potent adjuvant than CtxB, stimulating responses to hen egg lysozyme when the two were coadministered to mice intranasally, as assessed by enhanced serum and secretory antibody titers as well as by stimulation of lymphocyte proliferation in spleen and draining lymph nodes. These results indicate that, although structurally very similar, EtxB and CtxB have strikingly different immunostimulatory properties and should not be considered equiv. as prospective **vaccine** adjuvants.
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 3 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:205772 HCAPLUS

DOCUMENT NUMBER: 135:286925
TITLE: Immunomodulation using bacterial enterotoxins
AUTHOR(S): Simmons, C. P.; Ghaem-Magami, M.; Petrovska, L.; Lopes, L.; Chain, B. M.; **Williams, N. A.**; Dougan, G.
CORPORATE SOURCE: Department of Biochemistry, Imperial College of Science Technology and Medicine, London, SW7 2AZ, UK
SOURCE: Scandinavian Journal of Immunology (2001), 53(3), 218-226
CODEN: SJIMAX; ISSN: 0300-9475
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Immunol. unresponsiveness (tolerance) is a key feature of the mucosal immune system, and deliberate **vaccination** by a mucosal route can effectively induce immune suppression. However, some bacterial-derived proteins, e.g. cholera toxin and the heat labile toxin of Escherichia coli, are immunogenic and immunomodulatory at mucosal surfaces and can effectively adjuvant immune responses to codelivered bystander antigens. This review summarizes some of the structural and biol. characteristics of these toxins and provides examples of how these properties have been exploited for tolerance induction and mucosal **vaccine** development.
REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:100393 HCAPLUS
DOCUMENT NUMBER: 134:264842
TITLE: Protective mucosal immunity to ocular herpes simplex virus type 1 infection in mice by using Escherichia coli heat-labile enterotoxin B subunit as an adjuvant
AUTHOR(S): Richards, C. M.; Aman, A. T.; **Hirst, T. R.**; Hill, T. J.; **Williams, N. A.**
CORPORATE SOURCE: Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK
SOURCE: Journal of Virology (2001), 75(4), 1664-1671
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The potential of nontoxic recombinant B subunits of cholera toxin (rCtxB) and its close relative Escherichia coli heat-labile enterotoxin (rEtxB) to act as mucosal adjuvants for intranasal immunization with herpes simplex virus type 1 (HSV-1) glycoproteins was assessed. Doses of 10 .mu.g of rEtxB or above with 10 .mu.g of HSV-1 glycoproteins elicited high serum and mucosal anti-HSV-1 titers comparable with that obtained using CtxB (10 .mu.g) with a trace (0.5 .mu.g) of whole toxin (Ctx-CtxB). By contrast, doses of rCtxB up to 100 .mu.g elicited only meager anti-HSV-1 responses. As for Ctx-CtxB, rEtxB resulted in a Th2-biased immune response with high IgG1/IgG2a antibody ratios and prodn. of interleukin 4 (IL-4) and IL-10 as well as gamma interferon by proliferating T cells. The protective efficacy of the immune response induced using rEtxB as an adjuvant was

assessed following ocular challenge of immunized and mock-immunized mice. Epithelial disease was obsd. in both groups, but the immunized mice recovered by day 6 whereas mock-immunized mice developed more severe corneal disease leading to stromal keratitis. In addn., a significant redn. in the incidence of lid disease and zosteriform spread was obsd. in immunized animals and there was no encephalitis compared with 95% encephalitis in mock-immunized mice. The potential of such mucosal adjuvants for use in human **vaccines** against pathogens such as HSV-1 is discussed.

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:175834 HCAPLUS
DOCUMENT NUMBER: 132:217136
TITLE: Peptide fragments of cholera toxin B or enterotoxin B as immunomodulators and **vaccine** adjuvants and for the treatment of toxin-induced diarrhea
INVENTOR(S): Williams, Neil Andrew; **Hirst, Timothy Raymond**
PATENT ASSIGNEE(S): University of Bristol, UK
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000014114	A1	20000316	WO 1999-GB2970	19990907
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9957516	A1	20000327	AU 1999-57516	19990907
BR 9913501	A	20010605	BR 1999-13501	19990907
EP 1109828	A1	20010627	EP 1999-944696	19990907
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001001075	A	20010507	NO 2001-1075	20010302

PRIORITY APPLN. INFO.: GB 1998-19484 A 19980907
WO 1999-GB2970 W 19990907

AB A substance is provided which comprises any one or more of an amino acid sequence EVPGSQH, or a variant, homolog, fragment, deriv., or mimetic thereof. The substance is capable of acting in a manner that is the same as or is similar to enterotoxin B and/or cholera toxin B, but does not exhibit GM-1 binding activity. The substance may be used as an immunomodulator or **vaccine** adjuvant or for the treatment of toxin-induced diarrhea.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:736498 HCAPLUS
DOCUMENT NUMBER: 131:335799
TITLE: Immunomodulatory activity of B subunits of cholera toxin, verotoxin, and heat-labile enterotoxin
INVENTOR(S): **Hirst, Timothy Raymond**; Williams, Neil Andrew
PATENT ASSIGNEE(S): University of Bristol, UK
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958145	A2	19991118	WO 1999-GB1461	19990510
WO 9958145	A3	20000203		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9939394	A1	19991129	AU 1999-39394	19990510
BR 9910305	A	20010109	BR 1999-10305	19990510
EP 1075274	A2	20010214	EP 1999-922284	19990510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
GB 2353472	A1	20010228	GB 2000-27072	19990510
NO 2000005599	A	20010108	NO 2000-5599	20001106

PRIORITY APPLN. INFO.:

GB 1998-9958	A	19980508
GB 1998-11954	A	19980603
GB 1998-12316	A	19980608
WO 1999-GB1461	W	19990510

AB The authors disclose the use of: (i) heat-labile enterotoxin B subunit (EtxB), cholera toxin B subunit (CtxB) or verotoxin B subunit (VtxB) in **vaccine** prepns. to alter the immune response to pathogens. In one example, the secretory IgA response to herpes virus glycoproteins is enhanced by the adjuvant activity of EtxB. In addn., the authors disclose the use of agents other than EtxB or CtxB, which have ganglioside GM1-binding activity, or an agent other than VtxB which has globotriosylceramide (Gb3)-binding activity for affecting intracellular signaling events.

L8 ANSWER 7 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:495190 HCAPLUS

DOCUMENT NUMBER: 131:143512
TITLE: Verotoxin subunit B for modulating a glycosphingolipid-associated activity thus affecting an immune disorder
INVENTOR(S): Williams, Neil Andrew; **Hirst, Timothy Raymond**
PATENT ASSIGNEE(S): University of Bristol, UK
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9938530	A1	19990805	WO 1999-GB290	19990128
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2318190	AA	19990805	CA 1999-2318190	19990128
AU 9922900	A1	19990816	AU 1999-22900	19990128
EP 1049489	A1	20001108	EP 1999-902688	19990128
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: GB 1998-1871 A 19980128
WO 1999-GB290 W 19990128

AB The use of an agent in the manuf. of a medicament to affect an immune disorder is described. The agent is capable of modulating a glycosphingolipid assocd. activity. The modulation of the glycosphingolipid assocd. activity affects an immune disorder. Verotoxin B subunit is such an agent.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:231144 HCAPLUS
DOCUMENT NUMBER: 131:72385
TITLE: The major Epstein-Barr virus (EBV) envelope glycoprotein gp340 when incorporated into Iscoms primes cytotoxic T-cell responses directed against EBV lymphoblastoid cell lines
AUTHOR(S): **Wilson, A. D.**; Lovgren-Bengtsson, K.; Villacres-Ericsson, M.; Morein, B.; Morgan, A. J.
CORPORATE SOURCE: Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK
SOURCE: Vaccine (1999), 17(9-10), 1282-1290
CODEN: VACCDE; ISSN: 0264-410X

PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A recombinant form of the EBV envelope glycoprotein and **vaccine** candidate gp340, lacking its hydrophobic transmembrane region, was incorporated into Iscoms after coupling to phosphatidyl ethanolamine via carbohydrate residues. Coupling by partial oxidn. of gp340 carbohydrate with sodium periodate partly denatured the incorporated gp340 as indicated by its reduced reactivity with monoclonal antibodies that recognize the major neutralizing epitope. Immunization of cottontop tamarins with these Iscoms elicited antibody responses to gp340, but these antibodies only poorly recognized the major neutralizing epitope in a competition ELISA and were unable to neutralize EBV in vitro. Despite the lack of neutralizing antibody, immunization with these Iscoms primed significant in vitro proliferative responses to sol. gp340 in lymphocytes from the draining lymph nodes and spleen. T-cell lines were raised from both immunized and control animals by in vitro stimulation of peripheral blood lymphocytes or spleen cells with autologous EBV-transformed lymphoblastoid cell lines. The T-cell lines from control animals had higher nos. of CD4+ T-cells than CD8+ T-cells and were not cytotoxic for autologous lymphoblastoid cell lines (LCL). In contrast the lines from immunized animals contained more CD8+ T-cells than CD4+ T-cells and had marked cytotoxicity for autologous LCL.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:231143 HCAPLUS
DOCUMENT NUMBER: 131:72384
TITLE: Construction and murine immunogenicity of recombinant Bacille Calmette Guerin **vaccines** expressing the B subunit of Escherichia coli heat labile enterotoxin
AUTHOR(S): Hayward, Christopher M. M.; O'Gaora, Peadar; Young, Douglas B.; Griffin, George E.; Thole, Jelle; **Hirst, Timothy R.**; Castello-Branco, Luiz R. R.; Lewis, David J. M.
CORPORATE SOURCE: Division of Infectious Diseases, St. George's Hospital Medical School, London, SW17 0RE, UK
SOURCE: Vaccine (1999), 17(9-10), 1272-1281
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Three recombinant strains of Mycobacterium bovis Bacille Calmette Guerin (rBCG) were prepd. in which the immunogenic B subunit of human Escherichia coli heat labile enterotoxin (LT-Bh) was expressed either as a cytoplasm protein, a cell wall assocd. lipoprotein or a secreted protein. I.p. immunization of mice with these rBCG induced IgG and IgA antibodies to LT-Bh and shifted the serum IgG subclass response to subsequent challenge with purified LT-Bh from IgG1 to an IgG2a. Oral administration of recombinant BCG induced mucosal and serum IgA antibodies to LT-Bh which peaked four months after immunization. Antibody responses were greater when LT-Bh was expressed as a secreted protein or lipoprotein rather than

in the cytoplasm. Oral **vaccination** with recombinant BCG may be an effective approach, particularly to induce mucosal IgA and prime for a serum TH1 recall response.
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 10 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:499628 HCAPLUS
DOCUMENT NUMBER: 129:215366
TITLE: Indirect measurement of Epstein-Barr virus neutralizing antibodies by ELISA
AUTHOR(S): **Wilson, A. Douglas**; Morgan, Andrew J.
CORPORATE SOURCE: Department of Pathology and Microbiology, University of Bristol, Bristol, BS8 ITD, UK
SOURCE: J. Virol. Methods (1998), 73(1), 11-19
CODEN: JVMEDH; ISSN: 0166-0934
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A rapid and effective ELISA for measuring Epstein-Barr virus (EBV)-neutralizing antibodies in human sera was devised to replace the existing cumbersome method involving the inhibition of fetal cord blood B-cell transformation by the virus. The new method will be invaluable for assessing antibody responses in human subjects participating in EBV gp340 **vaccine** trials. The ELISA developed uses the human serum antibody to be tested to inhibit standardized binding of an EBV-neutralizing monoclonal antibody (mAb) to gp340 itself or its recombinant derivs. A serum which has high EBV-neutralizing antibody titers inhibits the binding of neutralizing mAb to gp340 more than a serum with low levels. EBV neutralization antibody titers obtained by the new inhibition ELISA correlate well with values obtained using the lengthy conventional assay where inhibition of B-cell transformation is assessed. The new assay can be carried out in a few hours compared to 4-5 wk for the conventional test and could be automated for processing very large sample nos. in **vaccine** trials.

L8 ANSWER 11 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:376129 HCAPLUS
DOCUMENT NUMBER: 129:160365
TITLE: Induction of mucosal immunity against herpes simplex virus type 1 in the mouse protects against ocular infection and establishment of latency
AUTHOR(S): Richards, C. M.; Shimeld, C.; **Williams, N. A.**; Hill, T. J.
CORPORATE SOURCE: Department of Pathology, University of Bristol, Bristol, BS8 1TD, UK
SOURCE: J. Infect. Dis. (1998), 177(6), 1451-1457
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immune responses were assessed after intranasal immunization of mice with a mixt. of herpes simplex virus type 1 (HSV-1) glycoproteins with cholera toxin and its B subunit as adjuvant. Antigen-specific serum antibodies,

which were largely IgG with IgG1 the major subclass, neutralized virus in vitro with a titer equiv. to that elicited by active infection. Significant levels of antigen-specific IgA were found in mucosal fluids of the eye as well as the vagina. Lymphocytes from draining lymph nodes showed secondary proliferative responses when cultured with HSV-1 in vitro, in immunized mice only, with the prodn. of interleukin-2, interferon-.gamma., interleukin-4, and interleukin-5. After ocular challenge, immunized mice were protected against the development of severe eye disease, zosteriform spread, or encephalitis, whereas the incidence of clin. symptoms in mock-immunized mice was 83%, 74%, and 52%, resp. Finally, the incidence of latency was reduced from 88% to 13% after intranasal immunization.

L8 ANSWER 12 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:589381 HCAPLUS
DOCUMENT NUMBER: 127:261452
TITLE: Enhancement of the immune response to non-replicating herpes simplex virus type-1 preparations by mucosal administration in the presence of cholera toxin
AUTHOR(S): Richards, C. M.; Hill, T. J.; **Williams, N. A.**
CORPORATE SOURCE: Department of Pathology and Microbiology, School of Medical Sciences, University of Bristol, Bristol, BS8 1TD, UK
SOURCE: Vaccine (1997), 15(10), 1065-1069
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

Claims 3-6, 25,

AB Different immunization regimes were compared to enhance the immune response following mucosal administration of non-replicating HSV-1 prepns. to mice. The serum anti-HSV Ig response following intragastric administration of heat or UV inactivated HSV-1 strain SC16 was compared with that elicited by an attenuated deriv. of SC16 (TKDM21). The highest response followed immunization with TKDM21 and this was markedly enhanced by repeated intragastric administration, reaching ca 35% of that elicited following a cutaneous infection with live virus. Repeated doses of killed virus produced only a minimal increase in the response even when given intranasally (i.n.). However, cholera toxin and its B-subunit with UV-inactivated virus or a mixt. of purified viral glycoproteins enhanced the anti-HSV response after i.n. immunization and produced antibody levels equiv. to those following intragastric delivery of live TKDM21.

L8 ANSWER 13 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:228375 HCAPLUS
DOCUMENT NUMBER: 126:262894
TITLE: Influence of Quillaja saponaria triterpenoid content on the immunomodulatory capacity of Epstein-Barr virus iscoms
AUTHOR(S): Dotsika, E.; Karagouni, E.; Sundquist, B.; Morein, B.; **Morgan, A.**; Villacres-Eriksson, M.
CORPORATE SOURCE: Hellenic Pasteur Institute, Athens, 115 21, Greece
SOURCE: Scand. J. Immunol. (1997), 45(3), 261-268
CODEN: SJIMAX; ISSN: 0300-9475
PUBLISHER: Blackwell

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The immune responses to immunostimulating complexes (iscoms) contg. recombinant Epstein-Barr virus (EBV) gp340 envelope protein was evaluated in BALB/c (H-2d) and CBA (H-2k) mice. Gp340-iscoms were used either with a low content of Quillaja triterpenoid adjuvant (L-iscoms) or supplemented with addnl. Quillaja adjuvant in the form of iscomatrix (S-iscoms). Class and subclass distribution of anti-gp340 antibodies, EBV-neutralizing antibodies, antigen-specific T cell proliferation and cytokine prodn. were detd. and these results compared to those obtained by immunization with non-adjuvated gp340. The H-2d and H-2k mice were characterized as low or high responders in respect to the level of specific anti-gp340 antibodies, secretion of IgG2a isotype, antigen-specific lymphoproliferative capacity, interferon-.gamma. (IFN-.gamma.) and interleukin-10 (IL-10) prodn. in the basic immunizations with gp340. While presentation of the antigen in iscom formulations with low levels of Quillaja triterpenoids induces a moderate enhancement of the immune responses in the low responder H-2d mice, supplementation with high levels of iscomatrix immunomodulator was required to enhance the immune responses in the high responder H-2k mice. In both mouse strains s.c. immunization with S-iscoms resulted in a significant increase of IgG1- and IgG2a-specific antibodies, as well as in strong antigen-specific proliferative response confirmed by the simultaneous cytokine prodn. The enhanced antigen-specific secretion of IL-2 and IFN-.gamma. together with the abrogation of IL-10 and the absence of IL-4 indicates that the responses were driven towards a Th1-type rather than Th2-type immune response. The S-iscom formulations minimized the differences in immune responses between the two mouse strains, but the capacity of immune sera to neutralize EBV transformation in vitro remained completely strain-dependent. These data indicate that immune responses generated by iscoms can be manipulated by altering the triterpenoid compn. of the iscoms and that the levels of triterpenoids can det. whether or not a Th1-type response is made.

L8 ANSWER 14 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:181160 HCAPLUS
DOCUMENT NUMBER: 126:170385
TITLE: Therapeutic agents and autoimmune diseases
INVENTOR(S): Williams, Neil Andrew; **Hirst, Timothy Raymond** ; Nashar, Toufic Osman
PATENT ASSIGNEE(S): University of Bristol, UK; Williams, Neil, Andrew; Hirst, Timothy, Raymond; Nashar, Toufic, Osman
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9702045	A1	19970123	WO 1996-GB1614	19960705

W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD,

SE, SG
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA

CA 2225788	AA	19970123	CA 1996-2225788	19960705	
AU 9663142	A1	19970205	AU 1996-63142	19960705	
EP 841939	A1	19980520	EP 1996-922162	19960705	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI					
CN 1192693	A	19980909	CN 1996-196258	19960705	
JP 11508586	T2	19990727	JP 1996-504927	19960705	
NO 9800005	A	19980305	NO 1998-5	19980102	
PRIORITY APPLN. INFO.:			GB 1995-13733 A	19950705	
			WO 1996-GB1614 W	19960705	

AB There is disclosed the use, as an agent in the treatment or the prevention of an autoimmune disease, of: (i) an agent having GM-1 binding activity, other than Ctx or Etx, or the B subunits of Ctx and Etx; or (ii) an agent having an effect on GM-1 mediated intracellular signalling events, but no GM-1 binding activity. These agents may also be used in the treatment of human T cell leukemia, in the prevention of transplant rejection or GVHD or in a **vaccination** method for **vaccinating** a mammalian subject.

L8 ANSWER 15 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:585846 HCAPLUS
DOCUMENT NUMBER: 125:265362
TITLE: Construction, purification and immunogenicity of antigen-antibody-LTB complexes
AUTHOR(S): Green, E. A.; Botting, C.; Webb, H. M.; **Hirst, T. R.**; Randall, R. E.
CORPORATE SOURCE: School Biological and Medical Sciences, University St. Andrews, KY 16 9AL, UK
SOURCE: Vaccine (1996), 14(10), 949-958
CODEN: VACCDE; ISSN: 0264-410X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An oligonucleotide, encoding a short epitope peptide tag, termed Pk, was inserted at the 3'-end of the gene coding B-subunit of Escherichia coli heat-labile enterotoxin (LTB). The presence of the Pk epitope on LTB-Pk was used to construct novel macromol. assemblies comprising LTB-Pk, an anti-Pk mAb, (mAb SV5-P-k) and Pk-linked recombinant SIV proteins. The 1:1:1 stoichiometry of such complexes was ensured by binding LTB-Pk to one arm of mAb SV5-P-k and an SIV-Pk antigen to the other arm of the antibody. Such SIV-mAb-LTB macromol. complexes bound to GM1-ganglioside in vitro, and when immunized systemically into mice were highly immunogenic, inducing both humoral and cell-mediated responses to the recombinant SIV antigens.

L8 ANSWER 16 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:1001766 HCAPLUS
DOCUMENT NUMBER: 124:23663
TITLE: Kinetics of acid-mediated disassembly of the B subunit pentamer of Escherichia coli heat-labile enterotoxin. Molecular basis of pH stability
AUTHOR(S): Ruddock, Lloyd W.; Ruston, Stephen P.; Kelly, Sharon

M.; Price, Nicholas C.; Freedman, Robert B.; **Hirst, Timothy R.**
CORPORATE SOURCE: Biol. Laboratory, Univ. Kent, Canterbury, Kent, CT2 7NJ, UK
SOURCE: J. Biol. Chem. (1995), 270(50), 29953-8
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The B-subunit pentamer of Escherichia coli heat-labile enterotoxin (EtxB) is highly stable, maintaining its quaternary structure in a range of conditions that would normally be expected to cause protein denaturation. In this paper the structural stability of EtxB has been studied as a function of pH by electrophoretic, immunochem., and spectroscopic techniques. Disassembly of the cyclic pentameric structure of human EtxB occurs only below pH 2. As detd. by changes in intrinsic fluorescence this process follows first-order kinetics, with the rate const. for disassembly being proportional to the square of the H+ ion concns., and with an activation energy of 155 kJ mol-1. A C-terminal deletion mutant, hEtxB214, similarly shows first-order kinetics for disassembly but with a higher pH threshold, resulting in disassembly being seen at pH 3.4 and below. These findings are consistent with the rate-limiting step for disassembly of human EtxB being the simultaneous disruption of two interfaces by protonation of two C-terminal carboxylates. By comparison, disassembly of the B-subunit of cholera toxin (CtxB), a protein which shows 80% sequence identity with EtxB, exhibits a much lower stability to acid conditions; with disassembly of CtxB occurring below pH 3.9, with an activation energy of 81 kJ mol-1. Reasons for the obsd. differences in acid stability are discussed, and the implications of these findings to the development of oral **vaccines** using EtxB and CtxB are considered.

claim1

L8 ANSWER 17 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:970087 HCAPLUS
DOCUMENT NUMBER: 124:53089
TITLE: Cholera and pertussis toxins, but not forskolin or LT-B, adjuvant IgA antibody responses to orally administered antigen
AUTHOR(S): **Wilson, A. D.**; Robinson, A.; Irons, L.; Stokes, C. R.; Bland, P. W.
CORPORATE SOURCE: Department of Veterinary Medicine, University of Bristol, Bristoe, BS18 7DU, UK
SOURCE: Adv. Exp. Med. Biol. (1995), Volume Date 1995, 371B, 1523-6
CODEN: AEMBAP; ISSN: 0065-2598
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors examd. the requirements for the optimal induction of IgA using pertussis toxin (PT) as an adjuvant. The results indicate that cholera toxin and PT possibly act by different mechanisms.

L8 ANSWER 18 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:740343 HCAPLUS
DOCUMENT NUMBER: 123:225829
TITLE: Immunoregulatory role of H-2 and intra-H-2 alleles on

antibody responses to recombinant preparations of B-subunits of Escherichia coli heat-labile enterotoxin (rEtxB) and cholera toxin (rCtxB)
AUTHOR(S): Nashar, Toufic O.; **Hirst, Timothy R.**
CORPORATE SOURCE: Res. Sch. Biosci., Univ. Kent Canterbury, Canterbury, CT2 7NJ, UK
SOURCE: Vaccine (1995), 13(9), 803-10
CODEN: VACCDE; ISSN: 0264-410X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The immunoregulatory role of H-2 and intra-H-2 alleles on antibody responses to recombinant prepns. of B-subunits of Escherichia coli heat-labile enterotoxin (rEtxB) and cholera toxin (rCtxB) is reported. Oral delivery of rEtxB to congenic mice of several different H-2 haplotypes resulted in H-2 dependent serum IgG responses (H-2d>H-2b=H-2q>H-2a>H-2k) and a similar spectrum of intestinal IgA responses in those strains tested. Responses to rEtxB and rCtxB were found to be differentially modulates by the H-2 locus, with significant differential effects in H-2b and H-2d congenic strains (H-2d>H-2b for rEtxB; H-2b>H-2d for rCtxB). Addnl., it was found that when rEtxB was fed to mice previously primed (orally) with either rEtxB or rCtxB only when rEtxB was fed to mice previously primed (orally) with either rEtxB or rCtxB or only those mice primed with rEtxB exhibited a booster response. A second booster immunization with rEtxB in rCtxB-primed mice produced an H-2 dependent spectrum of responses characteristic of those elicited by rEtxB, with the antibodies predominantly directed against rEtxB and not rCtxB. These results indicate that the differential response to rEtxB and rCtxB is set at the T- and B-cell level. Also, immunoregulation of antibody responses to rEtxB by intra-H-2 I-E in mice transgenic for the entire IE.alpha.k gene was investigated. No significant difference between responses in transgene-pos. and -neg. mice was found, suggesting that antigen presentation does not involve I-E, but occurs in the context of I-A. The implications of these results for the design of **vaccines** against enterotoxigenic E. coli and cholera diarrhea are discussed.

L8 ANSWER 19 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:404758 HCAPLUS
DOCUMENT NUMBER: 122:158078
TITLE: Preparation of a fusion protein for **vaccination** against Escherichia coli enterotoxins
AUTHOR(S): Eaglestone, S.; **Hirst, T. R.**
CORPORATE SOURCE: Res. Sch. of Biosciences, Univ. of Kent, Canterbury/Kent, CT2 7NJ, UK
SOURCE: Biochem. Soc. Trans. (1995), 23(1), 54S
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A recombinant fusion protein was prepd. as **vaccine** for enhancing immunity againsts Escherichia coli enterotoxins. The recombinant fusion protein comprises the B subunit C-terminal of cholera-like heat-labile enterotoxin and the hydrophobic C-terminal domain of the heat-stable enterotoxin.

L8 ANSWER 20 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:28693 HCAPLUS
DOCUMENT NUMBER: 122:53460
TITLE: Individuals from different populations identify multiple and diverse T-cell determinants on mycobacterial HSP70
AUTHOR(S): Adams, E.; Britton, W.; **Morgan, A.**; Sergeantson, S.; Basten, A.
CORPORATE SOURCE: Centenary Institute Cancer Medicine and Cell Biology, Newtown, Australia
SOURCE: Scand. J. Immunol. (1994), 39(6), 588-96
CODEN: SJIMAX; ISSN: 0300-9475
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The 70 kDa heat-shock protein (HSP) of Mycobacterium leprae stimulates both cellular and antibody responses in leprosy patients and subclinically infected individuals despite partial homol. with host HSP70. Furthermore, mycobacterial HSP70 can act as a carrier protein in unprimed mice, suggesting the presence of widely shared T-cell determinants on this protein. In order to elucidate the frequency and genetic restriction of these T-cell epitopes, we have undertaken a systematic anal. of the proliferative responses to 20mer peptides encompassing the whole protein in different populations. Caucasian BCG **vaccinees** who responded to recombinant M. leprae HSP70 identified multiple scattered T-cell determinants, four of which were recognized by 60% of subjects in assocn. with a variety of HLA-DR haplotypes. When a group of Nepali leprosy and tuberculosis patients were tested, significant differences in the pattern of peptide recognition were obsd. The dominant peptides recognized by Caucasian subjects were infrequently reactive and other peptides were stimulatory, again in assocn. with a variety of HLA-DR phenotypes. The C-terminal 70 residues of the M. leprae HSP70 are specific to M. leprae and sera from lepromatous leprosy patients bind to this region. However, few T-cell determinants were identified in these residues, indicating that this region is unhelpful as a diagnostic tool for detecting M. leprae-specific T-cell responses. When compared with the equiv. regions of the human HSP70, the commonly recognized peptides showed significant differences in amino-acid sequence. When taken in conjunction with the failure of human HSP70 to stimulate M. leprae HSP70-reactive T-cell clones (E. Adams et al., unpublished observations), this finding indicates that the human T-cell response to this protein is largely directed at mycobacterial-specific determinants. The presence of multiple T-cell epitopes on M. leprae HSP70 with varied patterns of HLA-DR assocn. suggests that the whole protein is required for stimulating effective T-cell responses in genetically diverse populations.

L8 ANSWER 21 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:291556 HCAPLUS
DOCUMENT NUMBER: 120:291556
TITLE: Purification of the B-subunit oligomer of Escherichia coli heat-labile enterotoxin by heterologous expression and secretion in a marine Vibrio
AUTHOR(S): Amin, Tehmina; **Hirst, Timothy R.**
CORPORATE SOURCE: Biol. Lab., Univ. Canterbury, Kent, CT2 7NJ, UK

SOURCE: Protein Expression Purif. (1994), 5(2), 198-204
CODEN: PEXPEJ; ISSN: 1046-5928
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Heat-labile enterotoxins (Etx) are plasmid-encoded, multimeric proteins produced by certain diarrheagenic strains of Escherichia coli. The nontoxic, receptor-binding B subunit (EtxB) of such toxins may be useful as a component of **vaccines** against enterotoxigenic E. coli, or as a carrier for the delivery of heterologous epitopes to the mucosal immune system. Here the authors describe a simple method for the purifn. of EtxB from a marine vibrio harboring a broad-host range controlled expression vector contg. the EtxB gene. Induction of a EtxB resulted in its specific secretion to the medium, to a concn. of greater than 25 mg/L of culture. The techniques of ultrafiltration and hydrophobic interaction chromatog. were used to purify EtxB to homogeneity from the medium of this organism (with a yield of 60.7%). EtxB-epitope fusion proteins were also successfully expressed and secreted in this marine vibrio, suggesting that this system may be of general use in the prepn. of EtxB-based **vaccines**.

L8 ANSWER 22 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:104286 HCAPLUS
DOCUMENT NUMBER: 120:104286
TITLE: Identification of human T cell epitopes in the Mycobacterium leprae heat shock protein 70-kD antigen
AUTHOR(S): Adams, Elizabeth; Britton, W. J.; **Morgan, A.**; Goodsall, A. L.; Basten, A.
CORPORATE SOURCE: Centen. Inst. Cancer Med. Cell Biol., Univ. Sydney, Newtown, 2042, Australia
SOURCE: Clin. Exp. Immunol. (1993), 94(3), 500-6
CODEN: CEXIAL; ISSN: 0009-9104
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a no. of pathogens, heat shock proteins (hsp) stimulate humoral and cellular immune response despite significant sequence identity with host hsp. The 70 kDa hsp of Mycobacterium leprae, which shares 47% identity with human hsp70 at the protein level, elicited a T cell response in most M. bovis (Bacille Calmette-Guerin (BCG)) **vaccines** as well as leprosy and tuberculosis patients and their contacts. To locate T cell epitopes, DNA fragments encoding portions of the 70 kDa hsp were expressed in the vector pGEX-2T and tested for T cell reactivity in an in vitro proliferative assay. Cultures of peripheral blood mononuclear cells (PBMC) from BCG **vaccinees** indicated that the C-terminal half of the mol. contained multiple T cell epitopes, as the T cells from a majority of M. leprae hsp70-reactive individuals responded to C-344. Lower proportions of patients with paucibacillary leprosy (36%) and tuberculosis patients (16%) responded to C-344. The smaller C-142 fragment which includes the terminal 70 residues unique to M. leprae and is the target for the human antibody response elicited a cellular response in few patients and no **vaccinees**. To map T cell epitopes, two series of synthetic peptides encompassing the region 278-502 were prepd. Using overlapping 12mer and 20mer peptides, this region of the mol. was found to contain several potential T cell epitopes. The longer peptides gave a clearer indication of reactive sequences including regions of the

mol. which were not identified with the 12mer peptides. Fine mapping of reactive peptide pools using the 12mer peptides identified two T cell epitopes. Although both were located in regions of the mol. shared with M. tuberculosis, one appeared to be cross-reactive with the equiv. human sequence, and thus has the potential to initiate autoimmune responses.

L8 ANSWER 23 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:166938 HCAPLUS
DOCUMENT NUMBER: 118:166938
TITLE: Recombinant enterotoxins as **vaccines** against Escherichia coli-mediated diarrhea
AUTHOR(S): Aitken, R.; **Hirst, T. R.**
CORPORATE SOURCE: Dep. Microbiol., Univ. Glasgow, Glasgow, G12 8QQ, UK
SOURCE: Vaccine (1993), 11(2), 227-33
CODEN: VACCDE; ISSN: 0264-410X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A fusion protein, comprising the B subunit of the heat-labile enterotoxin and a portion of the precursor to the heat-labile enterotoxin of E. coli, was created by recombinant genetic techniques. It is exported successfully to the bacterial periplasm and assembles into pentamers which retain the ability to bind to GM1 ganglioside. Native toxin epitopes are displayed and the mol. can be easily purified from periplasmic exts. of cells expressing the gene fusion. Although the protein carries the natural sequence of the heat-stable enterotoxin, it is greatly attenuated in toxicity. Systemic immunization of mice or oral administration of the fusion elicits antibody responses against both classes of E. coli enterotoxin.

L8 ANSWER 24 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:166786 HCAPLUS
DOCUMENT NUMBER: 118:166786
TITLE: Current progress in the development of the B subunits of cholera toxin and Escherichia coli heat-labile enterotoxin as carriers for the oral delivery of heterologous antigens and epitopes
AUTHOR(S): Nashar, Toufic O.; Amin, Tehmina; Marcello, Alessandro; **Hirst, Timothy R.**
CORPORATE SOURCE: Biol. Lab., Univ. Kent, Canterbury/Kent, CT2 7NJ, UK
SOURCE: Vaccine (1993), 11(2), 235-40
CODEN: VACCDE; ISSN: 0264-410X
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 49 refs., on: the functional and structural properties of heat-labile enterotoxin (EtxB) and cholera toxin B subunit (CTB); attachment of heterologous antigens and epitopes onto EtxB and CTB; high-level prodn. of recombinant EtxB- and CTB-fusion proteins; immunomodulating properties CT and.

L8 ANSWER 25 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:149603 HCAPLUS
DOCUMENT NUMBER: 116:149603
TITLE: Development of an immunoassay using recombinant maltose-binding protein-STa fusions for quantitating

antibody responses against STa, the heat-stable enterotoxin of Escherichia coli
AUTHOR(S): Aitken, Robert; **Hirst, Timothy R.**
CORPORATE SOURCE: Dep. Genet., Univ. Leicester, Leicester, LE1 7RH, UK
SOURCE: J. Clin. Microbiol. (1992), 30(3), 732-4
CODEN: JCMIDW; ISSN: 0095-1137
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A set of fusion proteins contg. heat-stable enterotoxin (STa) and maltose-binding protein were engineered. These mols. were readily purified and used as solid-phase antigens in an ELISA to monitor anti-STa responses in mice immunized with a recombinant **vaccine** composed of STa and the B subunit of heat-labile enterotoxin.

L8 ANSWER 26 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:56942 HCAPLUS
DOCUMENT NUMBER: 114:56942
TITLE: Heat-labile toxin B subunit fusion proteins for use in **vaccines**
INVENTOR(S): **Hirst, Timothy Raymond**; Aitken, Rober
PATENT ASSIGNEE(S): University of Leicester, UK
SOURCE: Eur. Pat. Appl., 11 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 372928	A2	19900613	EP 1989-312713	19891206
EP 372928	A3	19900627		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 2004738	AA	19900607	CA 1989-2004738	19891206
WO 9006366	A1	19900614	WO 1989-GB1462	19891206
W: AU, DK, FI, HU, JP, NO, US				
AU 9047544	A1	19900626	AU 1990-47544	19891206
ZA 8909338	A	19900829	ZA 1989-9338	19891206
PRIORITY APPLN. INFO.:			GB 1988-28523	19881207
			GB 1989-13991	19890617
			WO 1989-GB1462	19891206

AB Fusion proteins contg. the ganglioside GM1-binding domain of the heat-labile enterotoxin of enterotoxigenic Escherichia coli are prepd. for use as the antigenic component of **vaccines**. The binding of the fusion proteins to membranes via the ganglioside-binding domain makes these fusion proteins effective mucosal immunogens. Chimeric genes for this domain and the E. coli heat-stable enterotoxin was prepd. and the fusion protein manufd. by expression of the gene in E. coli. The resulting protein formed a pentamer as expected for the heat-labile toxin, was recognized by antibodies to both toxins, and one form of the fusion protein (lacking the first 48 amino acids of the heat-stable toxin) was non-toxic in mice at 725 ng/animal. The fusion protein was antigenic in rabbits and raised antibodies to both toxins (no data).

L8 ANSWER 27 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:55555 HCAPLUS
DOCUMENT NUMBER: 110:55555
TITLE: In vitro T cell responses to a candidate Epstein-Barr virus **vaccine**: human CD4+ T cell clones specific for the major envelope glycoprotein gp340
AUTHOR(S): Ulaeto, David; Wallace, Lesley; **Morgan, Andrew** ; Morein, Bror; Rickinson, Alan B.
CORPORATE SOURCE: Dep. Cancer Stud., Univ. Birmingham, Birmingham, B15 2TJ, UK
SOURCE: Eur. J. Immunol. (1988), 18(11), 1689-97
CODEN: EJIMAF; ISSN: 0014-2980
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Specific T cell proliferation was obsd. in short-term blood mononuclear cell cultures set up from Epstein-Barr virus (EBV)-immune individuals and challenged either with UV-irradiated EB virions or with a candidate subunit **vaccine** prepn., the purified envelope glycoprotein gp340 incorporated into immune stimulating complexes (gp340 iscoms). Limiting diln. culture of the activated T lymphoblasts in interleukin 2-contg. medium generated stable CD3+CD4+CD8- T cell clones. Three gp340 iscoms-induced clones from EBV-immune donor CG responded specifically to restimulation either with UV-EBV or with purified gp340 iscoms in the presence of autologous antigen-presenting cells (APC). Both T cell-depleted blood mononuclear cells and the EBV-transformed B cell line (treated with Acyclovir to block endogenous gp340 prodn.) could be used for presentation, the latter being the more efficient when gp340 iscoms was the source of antigen. All three gp340-specific CG clones were restricted through the HLA-DR2 antigen. One gp340 iscoms-induced clone from another EBV-immune donor, MR, likewise showed gp340-specific proliferation, in this case restricted through a HLA-DR4 antigen.

L8 ANSWER 28 OF 28 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1987:28350 HCAPLUS
DOCUMENT NUMBER: 106:28350
TITLE: Immunoactive chimeric ST-LT enterotoxins of Escherichia coli generated by in vitro gene fusion
AUTHOR(S): Sanchez, J.; Uhlin, B. E.; Grundstroem, T.; Holmgren, J.; **Hirst, T. R.**
CORPORATE SOURCE: Dep. Med. Microbiol., Univ. Goeteborg, Goeteborg, S-413 46, Swed.
SOURCE: FEBS Lett. (1986), 208(2), 194-8
CODEN: FEBLAL; ISSN: 0014-5793
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Two different lengths of the gene encoding E. coli heat-stable toxin (STa) were fused to the carboxy end of the gene coding for the E. coli heat-labile toxin A-subunit (LTA). The hybrid genes directed expression of chimeric LTA-STa proteins. Assocn. of these chimeras with native heat-labile toxin B-subunit (LTB) resulted in protein complexes that bound to GM1 ganglioside and thereby could be assayed in a GM1 ELISA. The complexes reacted with monoclonal antibodies against either LTA, LTB or STa indicating that the STa and LT epitopes remained immunol. intact after infusion. Genetically constructed chimeric proteins exhibiting LT and STa

antigens on the same mol. may represent a promising approach to development of broadly protective immunoprophylactic agents and(or) useful immunodiagnostic reagents for diarrheal diseases caused by enterotoxinogenic E. coli.

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information on CAS roles, enter HELP ROLES at an arrow prompt or use
the CAS Roles thesaurus (/RL field) in this file.

=> d stat que
L2          126 SEA FILE=REGISTRY (E OR ESCHERICHIA)(W)COLI(L)ENTEROTOXIN?
L3          127 SEA FILE=REGISTRY CHOLERA(L)TOXIN?
L4            1 SEA FILE=REGISTRY CHOLERATOXIN/BI
L5            1 SEA FILE=REGISTRY "CHOLERA TOXINS"/CN
L6            1 SEA FILE=REGISTRY "CHOLERA TOXINS"/CN
L7           12 SEA FILE=REGISTRY (E OR ESCHERICHIA)(W)COLI(L)VEROTOXIN?
L8            2 SEA FILE=REGISTRY GM1/CN
L9            2 SEA FILE=REGISTRY (GM1-GANGLIOSIDE/CN OR "GM1-GANGLIOSIDE
                .BETA.-GALACTOSIDASE"/CN)
L10           4 SEA FILE=REGISTRY (GB3/CN OR "GB3 SYNTHASE"/CN OR "GB3
                SYNTHASE (RATTUS NORVEGICUS STRAIN SPRAGUE-DAWLEY)"/CN OR "GB3
                SYNTHETASE"/CN OR "GB3/CD77 SYNTHASE (HUMAN)"/CN)
L11        2356 SEA FILE=HCAPLUS L2 OR ETXB OR (E OR ESCHERICHIA)(W)COLI(L)ENTE
                ROTOXIN?
L12        7801 SEA FILE=HCAPLUS L3 OR L4 OR CHOLERA?(W)TOXIN? OR CHOLERATOXIN?
                 OR CTXB
L14        7801 SEA FILE=HCAPLUS L5 OR L12
L15         275 SEA FILE=HCAPLUS L6 OR L7 OR VTXB OR (E OR ESCHERICHIA)(W)COLI(
                3A)VEROTOXIN?
L16        3642 SEA FILE=HCAPLUS L8 OR L9 OR GM1(3W)GANGLIOSIDE?
L17         661 SEA FILE=HCAPLUS L10 OR GB3
L18         246 SEA FILE=HCAPLUS (L11 OR L12 OR L14 OR L15) AND (HERPES OR
                HEPATITIS OR MENINGIT? OR HSV OR NEISSERIA OR GONNORHEA? OR
                PNEUMO? OR LEGONELLA OR MYCOBACTER? OR TUBERCULOSIS OR
                CHLAMYDIA OR TRACHOMYTIS OR HIV?)
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L19 18 SEA FILE=HCAPLUS L18(L)(L16 OR L17)

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L19 ANSWER 1 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:241298 HCAPLUS
DOCUMENT NUMBER: 136:259574
TITLE: Receptor-based assays for pathogens
INVENTOR(S): Chtterjee, Subroto
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 15 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002037592	A1	20020328	US 1998-19435	19980205

AB A rapid, simple, and inexpensive sandwich enzyme-linked receptor-based immunodot assay detects pathogens or pathogenic products in test samples using receptors for a characteristic component of the pathogen. This assay is widely applicable because it is highly specific, it does not require special equipment, and the results can be obtained within a few hours with the naked eye. Since the lipid-based receptors have a long-shelf life, they can be easily stored and used for a long time. Staphylococcus enterotoxin B (SEB) was detected in human serum and urine using an enzyme-linked immunodot blot assay with digalactosylceramide immobilized on PVDF membranes and antibodies to SEB.

IT **71965-57-6**, Globotriosylceramide
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(as receptor for Staphylococcal enterotoxin A and verocytotoxin 2; receptor-based assays for pathogens or pathogenic products)

IT **37758-47-7, GM1 ganglioside**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(as receptor for **cholera toxin**; receptor-based assays for pathogens or pathogenic products)

L19 ANSWER 2 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:79888 HCAPLUS
DOCUMENT NUMBER: 136:246010
TITLE: Segregation of CD4 and CXCR4 into distinct lipid microdomains in T lymphocytes suggests a mechanism for membrane destabilization by human immunodeficiency virus
AUTHOR(S): Kozak, Susan L.; Heard, Jean Michel; Kabat, David
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, Oregon Health Sciences University, Portland, OR, 97201-3098, USA
SOURCE: Journal of Virology (2002), 76(4), 1802-1815
CODEN: JOVIAM; ISSN: 0022-538X
PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent evidence has suggested that plasma membrane sphingolipids and cholesterol spontaneously coalesce into raft-like microdomains and that specific proteins, including CD4 and some other T-cell signaling mols., sequester into these rafts. In agreement with these results, we found that CD4 and the assocd. Lck tyrosine kinase of peripheral blood mononuclear cells and H9 leukemic T cells were selectively and highly enriched in a low-d. lipid fraction that was resistant at 0.degree.C to the neutral detergent Triton X-100 but was disrupted by extn. of cholesterol with filipin or methyl-.beta.-cyclodextrin. In contrast, the CXCR4 chemokine receptor, a coreceptor for X4 strains of human immunodeficiency virus type 1 (**HIV**-1), was almost completely excluded from the detergent-resistant raft fraction. Accordingly, as detd. by immunofluorescence with confocal microscopy, CD4 and CXCR4 did not coaggregate into antibody-induced cell surface patches or into patches of CXCR4 that formed naturally at the ruffled edges of adherent cells. The CXCR4 fluorescent patches were extd. with cold 1% Triton X-100, whereas the CD4 patches were resistant. In stringent support of these data, CD4 colocalized with patches of **cholera toxin** bound to the raft-assocd. sphingoglycolipid GM1, whereas CXCR4 did not. Addn. of the CXCR4-activating chemokine SDF-1.alpha. did not induce CXCR4 movement into rafts. Moreover, binding of purified monomeric gp120 envelope glycoproteins from strains of **HIV**-1 that use this coreceptor did not stimulate detectable redistributions of CD4 or CXCR4 between their sep. membrane domains. However, adsorption of multi-valent gp120-contg. **HIV**-1 virion particles appeared to destabilize the local CD4-contg. rafts. Indeed, adsorbed **HIV**-1 virions were detected by immunofluorescence microscopy and were almost all situated in nonraft regions of the cell surface. We conclude that **HIV**-1 initially binds to CD4 in a raft domain and that its secondary assocns. with CXCR4 require shifts of proteins and assocd. lipids away from their preferred lipid microenvironments. Our evidence suggests that these changes in protein-lipid interactions destabilize the plasma membrane microenvironment underlying the virus by at least several kilocalories per mol, and we propose that this makes an important contribution to fusion of the viral and cellular membranes during infection. Thus, binding of **HIV**-1 may be favored by the presence of CD4 in rafts, but the rafts may then disperse prior to the membrane fusion reaction.

IT **37758-47-7**, Ganglioside GM1
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CD4 and CXCR4 segregation into distinct lipid microdomains in T lymphocytes through **HIV** mediated membrane destabilization)

REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 3 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:809447 HCAPLUS
DOCUMENT NUMBER: 132:283982
TITLE: Formulation of **HIV**-envelope protein with lipid vesicles expressing ganglioside GM1 associated to **cholera toxin** B enhances mucosal immune responses
AUTHOR(S): Lian, Tianshun; Bui, Tot; Ho, Rodney J. Y.

CORPORATE SOURCE: Department of Pharmaceutics, School of Pharmacy, University of Washington, Seattle, WA, 98195-7610, USA
SOURCE: Vaccine (1999), 18(7-8), 604-611
CODEN: VACCDE; ISSN: 0264-410X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Taking advantage of the ability of pentameric **cholera toxin** B subunit (CTB) to bind selectively to GM1, we developed recently a CTB-mediated GM1 lipid vesicle delivery system to target drugs and proteins to mucosal tissues. In this report, we present the use of such a strategy to deliver an **HIV** envelope protein (**HIV** -env) to mucosal tissues via intranasal route. Intranasal administration of a recombinant **HIV** envelope protein formulated in CTB-assocd. GM1 lipid vesicles enhanced mucosal IgA antibody responses detected in the nasal and gut tissues, compared to that of control animals immunized with antigen formulated in GM1-free vesicles with CTB or formulated in alum-assocd. vesicles with CTB. We found a nearly 2- to 3-fold enhancement in IgA antibody titers detected both in nasal and gut tissues using the CTB-GM1 lipid vesicle delivery system, compared to using the GM1-free lipid vesicle system. Intranasal administration of **HIV** -env formulated in the CTB-assocd. GM1 vesicles also induced a significant level of serum IgG and cellular immune responses against **HIV** -env. IgG isotype anal. indicates that CTB in GM1 vesicle delivery system enhanced both IgG1 and IgG2a while CTB in alum formulation enhanced only IgG1. However, IgA and IgG antibody responses against CTB were similar for GM1 vesicles regardless of whether **HIV**-env was present in the vaccine formulation. Collectively, these data indicate that delivery of **HIV**-env to mucosal epithelial cells with CTB-assocd. GM1 lipid vesicles enhanced mucosal and systemic immune responses against the **HIV**-envelope protein. It is possible that both the CTB-mediated targeted delivery of antigen-loaded GM1 lipid vesicles and mucosal adjuvanticity of CTB may be involved in enhancing the immune responses.

IT **37758-47-7**, Ganglioside gm1
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(formulation of **HIV**-envelope protein with lipid vesicles expressing ganglioside GM1 assocd. with **cholera toxin** B enhances mucosal immune responses)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 4 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:736498 HCAPLUS
DOCUMENT NUMBER: 131:335799
TITLE: Immunomodulatory activity of B subunits of **cholera toxin**, verotoxin, and heat-labile enterotoxin
INVENTOR(S): Hirst, Timothy Raymond; Williams, Neil Andrew
PATENT ASSIGNEE(S): University of Bristol, UK
SOURCE: PCT Int. Appl., 63 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9958145	A2	19991118	WO 1999-GB1461	19990510
WO 9958145	A3	20000203		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9939394	A1	19991129	AU 1999-39394	19990510
BR 9910305	A	20010109	BR 1999-10305	19990510
EP 1075274	A2	20010214	EP 1999-922284	19990510
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
GB 2353472	A1	20010228	GB 2000-27072	19990510
NO 2000005599	A	20010108	NO 2000-5599	20001106

PRIORITY APPLN. INFO.:
GB 1998-9958 A 19980508
GB 1998-11954 A 19980603
GB 1998-12316 A 19980608
WO 1999-GB1461 W 19990510

AB The authors disclose the use of: (i) heat-labile enterotoxin B subunit (**EtxB**), **cholera toxin** B subunit (**CtxB**) or verotoxin B subunit (**VtxB**) in vaccine prepns. to alter the immune response to pathogens. In one example, the secretory IgA response to **herpes** virus glycoproteins is enhanced by the adjuvant activity of **EtxB**. In addn., the authors disclose the use of agents other than **EtxB** or **CtxB**, which have ganglioside GM1-binding activity, or an agent other than **VtxB** which has globotriosylceramide (**Gb3**)-binding activity for affecting intracellular signaling events.

IT **37758-47-7**, Ganglioside GM1 **71965-57-6**, Globotriosylceramide
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(immunomodulators with signaling activity mediated via binding to)

L19 ANSWER 5 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:148593 HCAPLUS
DOCUMENT NUMBER: 130:337314
TITLE: Human milk glycoconjugates that inhibit pathogens
AUTHOR(S): Newburg, David S.
CORPORATE SOURCE: Shriver Cent. Mental Retardation, Waltham, MA, 02452, USA
SOURCE: Curr. Med. Chem. (1999), 6(2), 117-127
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers

DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 33 refs. Breast-fed infants have lower incidence of diarrhea, respiratory disease, and otitis media. The protective effects of human milk have long been attributed to the presence of secretory IgA. Human milk contains large nos. and amts. of complex carbohydrates, including glycoproteins, glycolipids, glycosaminoglycans, mucins, and esp. oligosaccharides. Oligosaccharides are the third most abundant solid constituent of human milk and contain a myriad of structures. Complex carbohydrate moieties of glycoconjugates and oligosaccharides are synthesized by the many glycosyltransferases in the mammary gland. Those with homol. to cell surface glycoconjugate pathogen receptors may inhibit pathogen binding, thereby protecting the nursed infant. Several examples are reviewed, including a fucosyloligosaccharide inhibiting the diarrheagenic effects of stable toxin of Escherichia coli. A different fucosyloligosaccharide inhibits infection by Campylobacter jejuni. The binding of Streptococcus **pneumoniae** and enteropathogenic E. coli to their resp. receptors is inhibited by human milk oligosaccharides. The 46-kD glycoprotein, lactadherin, inhibits rotavirus binding and infectivity. Low levels of lactadherin in human milk are assocd. with a higher incidence of symptomatic rotavirus infections in breast-fed infants. A mannosylated glycopeptide inhibits the binding of enterohemorrhagic E. coli. A glycosaminoglycan inhibits binding of gp120 to CD4, the first step in **HIV** infection. Human milk mucin inhibits binding by S-fimbriated E. coli. The ganglioside GM1 inhibits diarrhea induced by **cholera toxin** and labile toxin of E. coli. The neutral glycosphingolipid **Gb3** binds to Shigatoxin. Thus, many complex carbohydrates of human milk may be novel antipathogenic agents. Milk glycoconjugates and oligosaccharides may be a major source of protection for breast-fed infants.
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L19 ANSWER 6 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:568970 HCAPLUS
DOCUMENT NUMBER: 129:200179
TITLE: Methods and compns. for detection of analytes using color changes that occur in biopolymeric material in response to selective binding of analytes
INVENTOR(S): Stevens, Raymond; Quan, Cheng
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: PCT Int. Appl., 121 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9836263	A1	19980820	WO 1998-US2777	19980213
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9861627	A1	19980908	AU 1998-61627	19980213

EP 1007943 A1 20000614 EP 1998-906389 19980213
R: CH, DE, FR, GB, LI
PRIORITY APPLN. INFO.: US 1997-38383P P 19970214
WO 1998-US2777 W 19980213

AB The present invention relates to methods and compns. for the direct detection of analytes using color changes that occur in biopolymeric material in response to selective binding of analytes. The invention provides biopolymeric materials comprising a plurality of polymd. self-assembling monomers and one or more protein ligands, wherein the biopolymeric materials change color in the presence of analyte. In some embodiments, the protein ligands are selected from the group consisting of peptides, proteins, antibodies, receptors, channels, and combinations thereof, although the present invention contemplates all protein ligands. In specific embodiments, the antibodies of the presently claimed invention are directed against **Chlamydia**.

IT **37758-47-7**, Ganglioside GM1
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(methods and compns. for detection of analytes using color changes that occur in biopolymeric material in response to selective binding of analytes)

L19 ANSWER 7 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:550561 HCAPLUS
DOCUMENT NUMBER: 129:172763
TITLE: Receptor-based assays for pathogens
INVENTOR(S): Chatterjee, Subroto
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9835233	A1	19980813	WO 1998-US1977	19980206
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9862627	A1	19980826	AU 1998-62627	19980206

PRIORITY APPLN. INFO.: US 1997-38145P P 19970210
US 1997-37553P P 19970211
WO 1998-US1977 W 19980206

AB A rapid, simple, and inexpensive sandwich enzyme-linked receptor based immunodot assay detects pathogens or pathogenic products in test samples using receptors for a characteristic component of the pathogen. This assay is widely applicable because it is highly specific, it does not require special equipment, and the results can be obtained within a few

hours with the naked eye. Since the lipid-based receptors have a long-shelf life, they can be easily stored and used for a long time. Digalactosylceramide was applied to polyvinylidene difluoride membrane and the membrane was blocked with bovine serum albumin before use in an immunodot blot assay to detect staphylococcal enterotoxin B (SEB). Bound SEB was detected by treatment with primary antibodies to SEB, alk. phosphatase-labeled secondary antibodies, and enzyme substrate.

IT **37758-47-7, GM1 ganglioside 71965-57-6**
, Globotriosylceramide
RL: ARG (Analytical reagent use); THU (Therapeutic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(as receptor; receptor-based assays for pathogens)

L19 ANSWER 8 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:106056 HCAPLUS
DOCUMENT NUMBER: 128:164726
TITLE: Polymeric assemblies for sensitive colorimetric assays
INVENTOR(S): Charych, Deborah
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9804743	A1	19980205	WO 1997-US13253	19970728
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9738973	A1	19980220	AU 1997-38973	19970728

PRIORITY APPLN. INFO.: US 1996-22942P P 19960729
WO 1997-US13253 W 19970728

AB The present invention relates to a method for direct detection of analytes using color changes in liposomes which occur in response to selective binding to analytes to their surface. The placement and selection of the polymerizable group in the monomer utilized as a precursor in colorimetric film and liposome prodn. improves sensitivity and also provides a final color change reaction which is specific to an exact analyte concn.

IT **104443-62-1**, Ganglioside GM1
RL: NUU (Other use, unclassified); USES (Uses)
(polymeric assemblies for sensitive colorimetric assays)

L19 ANSWER 9 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:207764 HCAPLUS
DOCUMENT NUMBER: 126:203696
TITLE: Nucleic acid composition with ganglioside GM1-binding

protein for delivery to mucosal, neural or other cells, nucleic acid expression, and immunomodulation or gene therapy
INVENTOR(S): King, Dannie H.
PATENT ASSIGNEE(S): Maxim Pharmaceuticals, USA
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9705267	A2	19970213	WO 1996-US12041	19960719
W: AU, CA, JP				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9665057	A1	19970226	AU 1996-65057	19960719
EP 840796	A2	19980513	EP 1996-924664	19960719
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 11510164	T2	19990907	JP 1996-507664	19960719

PRIORITY APPLN. INFO.: US 1995-1527P P 19950726
WO 1996-US12041 W 19960719

AB A compn. comprising a GM1-binding protein and a polynucleotide in assocn. with the binding protein is described for delivery of a polynucleotide to mucosal, neural, or other cells. A method is described for modulating immunity comprising administering the compn. to an animal and expressing the polynucleotide whereby the animal generates an immune response to the product of the polynucleotide. Also included is a method for gene therapy comprising administering to an animal a GM1-binding protein and a functional polynucleotide and expressing the polynucleotide in the animal whereby the function of the polynucleotide confers on the animal a therapeutic effect.

IT **37758-47-7**, Ganglioside GM1
RL: BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(mucosa-binding antibody against GM1 receptor; nucleic acid compn. with GM1 receptor-binding protein for delivery to mucosal, neural or other cells, nucleic acid expression, and immunomodulation or gene therapy)

L19 ANSWER 10 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:352577 HCAPLUS
DOCUMENT NUMBER: 125:29922
TITLE: **Mycobacterium** avium- and **Mycobacterium tuberculosis** -containing vacuoles are dynamic, fusion-competent vesicles that are accessible to glycosphingolipids from the host cell plasmalemma
AUTHOR(S): Russell, David G.; Dant, Jaime; Sturgill-Koszychi, Sheila
CORPORATE SOURCE: Department Molecular Microbiology, Washington University School Medicine, St. Louis, MO, 63110, USA
SOURCE: J. Immunol. (1996), 156(12), 4764-4773

CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The vacuoles inhabited by viable **Mycobacterium** avium and **Mycobacterium tuberculosis** show limited fusion with endosomal and lysosomal compartments. This ability to regulate the maturation of their phagosomal compartments and restrict their differentiation into hydrolytically active vacuoles appears to correlate with the survival of the bacilli. Data presented in this current study demonstrate that despite the apparent isolation of **mycobacterial** vacuoles from the lysosomal network, they are dynamic, fusion-competent vesicles. Exploiting the ability of **cholera toxin** B subunit to bind to **GM1 ganglioside** on the macrophage plasmalemma, we demonstrate that these glycosphingolipids have ready access to the **mycobacterial** vacuoles. Entry into **mycobacterial** vacuoles is rapid, within 5 min of addn. to the cells, and does not proceed through a brefeldin A-sensitive pathway. Furthermore, the gangliosides follow a route that differs from that taken by fluid-phase markers. TLC anal. of gangliosides isolated from **Mycobacterium**-contg. vacuoles, and IgG-bead phagosomes reveal similar profiles. These data indicate that rather than being fusion incompetent, **mycobacterial** vacuoles are actually highly dynamic, fusion-competent vesicles that behave like an extension of the recycling endosomal app.
IT **37758-47-7, GM1 ganglioside**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**Mycobacterium** avium- and **Mycobacterium tuberculosis**-contg. vacuoles are dynamic, fusion-competent vesicles that are accessible to ganglioside GM1 from the host cell plasmalemma)

L19 ANSWER 11 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:29588 HCAPLUS
DOCUMENT NUMBER: 124:108000
TITLE: Characterization of an internal permissive site in the **cholera toxin** B-subunit and insertion of epitopes from human immunodeficiency virus-1, **hepatitis** B virus and enterotoxigenic Escherichia coli
AUTHOR(S): Baeckstroem, Malin; Holmgren, Jan; Schoedel, Florian; Lebens, Michael
CORPORATE SOURCE: Dep. of medical Microbiology and Immunology, Goeteborg Univ., Goeteborg, Swed.
SOURCE: Gene (1995), 165(2), 163-71
CODEN: GENED6; ISSN: 0378-1119
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We previously described the construction of novel hybrid proteins based on the B-subunit of **cholera toxin** (CTB) [M. Baeckstroem et al., Gene 149 (1994) 211-217], in which a neutralizing B-cell epitope from the third variable (V3) loop in the envelope glycoprotein gp120 from human immunodeficiency virus type 1 (**HIV**-1) was inserted within a surface-exposed region between amino acids (aa) 55 and 64. The resulting protein retained properties of native CTB and could induce

strong anti-CTB antibody (Ab) responses, but the inserted gp120 epitope was only modestly immunogenic. In this study, the potential use of this internal permissive site in CTB for the insertion of heterologous epitopes has been further investigated. Six addnl. plasmids were constructed encoding **HIV**::CTB hybrid proteins with ten to fourteen aa from the V3 loop of gp120 genetically inserted at different positions between aa 52 and 65, with deletions of different CTB aa. Plasmids encoding proteins with peptides inserted between aa 53 and 64 in CTB gave rise to stable proteins which reacted with CTB-specific monoclonal antibodies (mAb) and bound to **GM1 gangliosides** (GM1), indicating that insertions between these positions do not drastically alter the conformation or the receptor-binding properties of native CTB. Plasmids were also constructed encoding CTB hybrid protein which had either an 11-aa peptide from **hepatitis** B virus (HBV) pre-S(2) or one of two peptides related to the heat-stable toxin (STa) of enterotoxigenic Escherichia coli inserted between aa 55 and 64 of CTB. This resulted in the prodn. of HBV::CTB or ST::CTB hybrid proteins and illustrated that the internal permissive site can be used for insertion of peptides of varying aa compn.

L19 ANSWER 12 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:840281 HCAPLUS
DOCUMENT NUMBER: 123:253944
TITLE: Gene fusion of **cholera toxin** B subunit and HBV PreS2 epitope and the antigenicity of fusion protein
AUTHOR(S): Shi, Cheng-hua; Cao, Cheng; Zhig, Jing-sheng; Li, Jiezhi; Ma, Qing-jun
CORPORATE SOURCE: Molecular Genetics Center, Institute Biotechnology, Beijing, 100850, Peop. Rep. China
SOURCE: Vaccine (1995), 13(10), 933-7
CODEN: VACCDE; ISSN: 0264-410X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A unique EcoRI site was introduced at the 3' end of **cholera toxin** B subunit (CTB) gene by site-directed mutagenesis and polynucleotides encoding 120-145aa epitope of HBV PreS2 were chem. synthesized and fused to the 3' end of **cholera toxin** B subunit gene. The fused gene was over-expressed (about 30 .mu.g mL-1) in E. coli, and more than 95% of the fusion protein was secreted into the medium. The fusion protein expressed was purified by affinity chromatog. The chimera protein obtained bound to ganglioside GM1, and had the antigenicity of both **cholera toxin** B subunit and HBV PreS2 as confirmed by ELISA. After mice were immunized i.m. with the fusion protein, anti-CTB antibody and anti-PreS2 antibody were produced. These results indicated that the fusion protein retained not only the biol. function of CTB but also the antigenicity and the immunogenicity of **cholera toxin** B subunit and HBV PreS2 epitope. This work provided a sound basis for further studies on the construction of engineered peptide vaccine.
IT **37758-47-7**, Ganglioside GM1
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(gene fusion of **cholera toxin** B subunit and **hepatitis** B virus PreS2 antigen epitope and antigenicity of

fusion protein in relation to vaccines and ganglioside GM1 binding)

L19 ANSWER 13 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:404765 HCAPLUS
DOCUMENT NUMBER: 122:233725
TITLE: Construction of a fusion protein between B subunit of **E. coli** heat-labile **enterotoxin** and the C-terminus of **herpes** simplex virus-DNA polymerase
AUTHOR(S): Loregian, Arianna; Marcello, Alessandro; Hirst, Timothy R.; Marsden, Howard S.; Palu, Giorgio
CORPORATE SOURCE: Institute of Microbiology, Univ. of Padova, Italy
SOURCE: Biochem. Soc. Trans. (1995), 23(1), 61S
CODEN: BCSTB5; ISSN: 0300-5127
DOCUMENT TYPE: Journal
LANGUAGE: English
AB It was recently reported that the B subunit of heat-labile **enterotoxin** from **Escherichia coli** (**EtxB**) could be used as a recombinant carrier for the receptor-mediated delivery of a peptide fused to it. This was further examd. here by characterizing the fusion protein obtained by genetically linking the C-terminal 27 amino acids of **HSV**-1 DNA polymerase to the C-terminus of **EtxB** (**EtxB**-DNApol). The novel polypeptide was overexpressed in **E. coli** XL1-Blue and shown to be translocated to the periplasmic compartment at an approx. 10-fold lower level than wild-type **EtxB** expressed under the same conditions. The same expt. also indicated that **EtxB**-DNApol was properly assembled into pentamers capable of binding GM1.
IT **37758-47-7**, Ganglioside GM1
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(binding by fusion protein; construction of a fusion protein between B subunit of **E. coli** heat-labile **enterotoxin** and C-terminus of **herpes** simplex virus-DNA polymerase)

L19 ANSWER 14 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:217631 HCAPLUS
DOCUMENT NUMBER: 122:29539
TITLE: Insertion of a **HIV**-1-neutralizing epitope in a surface-exposed internal region of the **cholera toxin** B-subunit
AUTHOR(S): Baeckstroem, Malin; Lebens, Michael; Schoedel, Florian; Holmgren, Jan
CORPORATE SOURCE: Department of Medical Microbiology and Immunology, University of Goeteborg, Goteborg, Swed.
SOURCE: Gene (1994), 149(2), 211-17
CODEN: GENED6; ISSN: 0378-1119
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The non-toxic B-subunit of **cholera toxin** (CTB) is a powerful immunogen and has been investigated as a carrier for foreign peptide epitopes, with peptides genetically fused to either the N- or C terminus of CTB. In the present study, the authors have constructed a plasmid encoding a novel intrachain CTB fusion protein with a peptide epitope inserted into an internal region of CTB: eight amino acids (aa) in

CTB (56-63) were substituted with a 10-aa peptide from the third variable (V3) loop of the **HIV**-1 envelope protein gp120. The resulting chimeric protein retained important functional characteristics of the native CTB including pentamerization and **GM1 ganglioside** receptor binding. The internal hybrid protein was also shown to be resistant to proteolytic degrdn. during prodn. in Vibrio cholerae, whereas a terminal hybrid protein, where the same gp120-epitope was fused to the N-terminus of CTB, was rapidly cleaved during culture. The inserted epitope, which is known to give rise to **HIV**-1 neutralizing Ab, could be detected with a V3 loop-specific monoclonal Ab when the chimeric protein was analyzed in ELISA and immunoblot, indicating that the epitope inserted at this site is presented on the surface of the protein. Consistent with these observations, immunization of mice with the CTB:: **HIV** hybrid protein elicited a high titered serum Ab response to the CTB moiety and also, in some but not all animals, a detectable response to the inserted gp120 epitope.

L19 ANSWER 15 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:595086 HCAPLUS
DOCUMENT NUMBER: 121:195086
TITLE: Specific inhibition of **herpes** virus replication by receptor-mediated entry of an antiviral peptide linked to **Escherichia coli enterotoxin** B subunit
AUTHOR(S): Marcello, Alessandro; Loregian, Arianna; Cross, Anne; Marsden, Howard; Hirst, Timothy R.; Palu, Giorgio
CORPORATE SOURCE: Institute of Microbiology, University of Padova, Padova, 35121, Italy
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1994), 91(19), 8994-8
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Mimetic peptides capable of selectively disrupting protein-protein interactions represent potential therapeutic agents for inhibition of viral and cellular enzymes. This approach was first suggested by the observation that the peptide YAGAVVNDL, corresponding to the carboxyl-terminal 9 amino acids of the small subunit of ribonucleotide reductase of **herpes** simplex virus, specifically inhibited the viral enzyme in vitro. Evaluation and use of this peptide as a potential antiviral agent has, however, been thwarted by its failure to inhibit virus replication in vivo, presumably because the peptide is too large to enter eukaryotic cells unaided. Here, we show that the nontoxic B subunit of **Escherichia coli** heat-labile **enterotoxin** can be used as a recombinant carrier for the receptor-mediated delivery of YAGAVVNDL into virally infected cells. The resultant fusion protein specifically inhibited **herpes** simplex virus type 1 replication and ribonucleotide reductase activity in quiescent Vero cells. Preincubation of the fusion protein with sol. **GM1 ganglioside** abolished this antiviral effect, indicating that receptor-mediated binding to the target cell is necessary for its activity. This provides direct evidence of the usefulness of carrier-mediated delivery to evaluate the intracellular efficacy of a putative antiviral peptide.

L19 ANSWER 16 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:252880 HCAPLUS
DOCUMENT NUMBER: 118:252880
TITLE: Intranasal immunization against **herpes** simplex virus infection by using a recombinant glycoprotein D fused with immunomodulating proteins, the B subunit of **Escherichia coli** heat-labile **enterotoxin** and interleukin-2
AUTHOR(S): Hazama, M.; Mayumi-Aono, A.; Miyazaki, T.; Hinuma, S.; Fujisawa, Y.
CORPORATE SOURCE: Biol. Res. Lab., Takeda Chem. Ind., Ltd., Osaka, 532, Japan
SOURCE: Immunology (1993), 78(4), 643-9
CODEN: IMMUAM; ISSN: 0019-2805
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To establish a novel strategy of mucosal immunization against **herpes** simplex virus type 1 (**HSV**-1) infection, the authors studied the immune responses elicited by intranasal immunization with several forms of a recombinant glycoprotein D (gD) of **HSV**-1. A truncated gD (t-gD) co-administered with heat-labile **enterotoxin** B subunit (LTB) from **E. coli** induced both a mucosal immune response involving secretion of anti-gD IgA and serum IgG prodn. The levels of these responses were comparable to those in mice which had recovered from intranasal **HSV**-1 infections. The fusion protein (t-gD-LTB), consisting of t-gD and LTB, induced the responses more efficiently than did co-administration of t-gD and LTB, although **GM1 ganglioside** binding activity was reduced in t-gD-LTB. The authors found that another fusion protein, consisting of t-gD and human interleukin-2 (t-gD-IL-2), also elicited antibody responses comparable to those induced by t-gD-LTB. Immunity acquired by intranasal immunization with t-gD-IL-2 protected mice from i.p. **HSV**-1 infections, whereas t-gD-LTB or t-gD alone failed to provide protection against infection. Even in a mouse strain that responded highly to s.c. administered gD, intranasally administered t-gD did not elicit antibody responses. The lack of response to gD was clearly abrogated by co-administration with IL-2, and administration of t-gD-IL-2 induced an excellent level of antibody responses in this strain. These results suggest that the IL-2 fusion strategy yields a new type of mucosal immunization, the mechanism of which differs from that speculated for the mucosal adjuvant activity of LTB.
IT **37758-47-7**, Ganglioside, GM1
RL: BIOL (Biological study)
(gD glycoprotein/enterotoxin fusion product binding to, immune response to **herpes** simplex virus following nasal immunization in relation to)

L19 ANSWER 17 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:610320 HCAPLUS
DOCUMENT NUMBER: 117:210320
TITLE: Vaccination by **cholera toxin** conjugated to a **herpes** simplex virus type 2 glycoprotein D peptide
AUTHOR(S): Drew, Murray D.; Estrada-Correa, Alberto; Underdown,

Brian J.; McDermott, Mark R.
CORPORATE SOURCE: Health Sci. Cent., McMaster Univ., Hamilton, ON, L8N 3Z5, Can.
SOURCE: J. Gen. Virol. (1992), 73(9), 2357-66
CODEN: JGVIAY; ISSN: 0022-1317
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunization of BALB/cJ mice with a peptide corresponding to residues 1-23 of glycoprotein D [gD(1-23)] from **herpes** simplex virus type 2 (**HSV**-2) elicits antibody responses which correlate with protection against lethal **HSV**-2 infection. The present study examd. the ability of **cholera toxin** (CTX) to act as an immunogenic carrier for gD(1-23). The no. of gD(1-23) residues conjugated to CTX affected its binding to **GM1 ganglioside** and physiol. toxicity, both of which are factors affecting oral immunogenicity. The antibody response elicited after i.p. immunization with the CTX-gD(1-23) conjugate was protective against a lethal i.p. challenge with **HSV**-2. In other expts., mice were immunized i.p. on day 0 and subsequent immunizations conducted on days 14 and 28 were administered either intragastrically or intravaginally (i.vag.). The i.p. priming followed by either i.p. or intragastric boosting resulted in anti-**HSV**-2 antibodies in vaginal washings and in protection against a lethal i.vag. challenge with **HSV**-2. The i.p. priming followed by i.vag. boosting did not elicit anti-**HSV**-2 antibodies in vaginal washings and did not protect mice against a lethal i.vag. challenge with **HSV**-2. These results suggest that CTX can act as a systemic and an oral delivery mol. for the covalently linked gD(1-23) peptide and that such conjugates can elicit protective immune responses against systemic and genital **HSV**-2 infection.
IT **37758-47-7**, Ganglioside GM1
RL: BIOL (Biological study)
(**cholera toxin** binding to, toxin conjugates with **herpes** simplex virus type 2 glycoprotein D peptide inhibition of, immunogenicity in relation to)

L19 ANSWER 18 OF 18 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1984:608659 HCAPLUS
DOCUMENT NUMBER: 101:208659
TITLE: Glycolipids of the mouse peritoneal macrophage. Alterations in amount and surface exposure of specific glycolipid species occur in response to inflammation and tumoricidal activation
AUTHOR(S): Mercurio, Arthur M.; Schwarting, Gerald A.; Robbins, Phillips W.
CORPORATE SOURCE: Cent. Cancer Res., Massachusetts Inst. Technol., Cambridge, MA, 02139, USA
SOURCE: J. Exp. Med. (1984), 160(4), 1114-25
CODEN: JEMEAV; ISSN: 0022-1007
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The major glycolipid constituents of the mouse peritoneal macrophage have been characterized and alterations were demonstrated in the amt. and in the accessibility of specific glycolipid species to galactose oxidase/NaB3H4 labeling, an indicator of glycolipid surface exposure,

which occur in response to inflammation and as a consequence of activation to a tumoricidal state. The key findings are: (a) Asialo GM1, a major neutral glycolipid constituent of all macrophage populations examd., is accessible to galactose oxidase/NaB3H4 labeling on the surface of thioglycollate (TG)-elicited and BCG-activated macrophages but not on resident macrophages; (b) **GM1** is the predominant **ganglioside** constituent of the mouse macrophage. Resident macrophages contain 2 distinct GM1 species, as detd. by **cholera toxin** binding, while TG-elicited and BCG-activated macrophages contain an addnl. GM1 species. Differences in the relative amts. of these GM1 species, as well as in their accessibility to galactose oxidase/NaB3H4 labeling, exist among the macrophage populations. These observations suggest that both a chem. and spatial reorganization of surface glycolipids occurs in response to inflammation and tumoricidal activation.

IT **37758-47-7 71965-57-6**
RL: BIOL (Biological study)
(of macrophage cell surface, inflammation and tumoricidal activation effect on)

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             ROTOXIN?) OR CTXB OR VTXB OR CHOLERA(W)TOXIN OR CHOLERATOXIN?
S2       3121   S1 AND (GM1 OR GM1(W)GANGLIOSIDE? OR GB3)
S3       1245   RD (unique items)
S4         41   S3 AND (HERPES OR HEPATITIS OR MENINGIT? OR HSV OR NEISSER-
               IA OR GONNORHEA? OR PNEUMO? OR LEGONELLA OR MYCOBACTER? OR TU-
               BERCULOSIS OR CHLAMYDIA OR TRACHOMYTIS OR HIV?)
?t4/3 ab/1-41
>>>No matching display code(s) found in file(s): 65

 4/AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12866651   21657456   PMID: 11799176
  Segregation of CD4 and CXCR4 into distinct lipid microdomains in T
lymphocytes suggests a mechanism for membrane destabilization by human
immunodeficiency virus.
  Kozak Susan L; Heard Jean Michel; Kabat David
  Department of Biochemistry and Molecular Biology, Oregon Health Sciences
University, Portland, Oregon 97201-3098, USA.
  Journal of virology (United States)  Feb 2002,  76  (4)  p1802-15,
ISSN 0022-538X  Journal Code: 0113724
  Contract/Grant No.: CA67358, CA, NCI
  Languages: ENGLISH
  Document type: Journal Article
  Record type: Completed
  Recent evidence has suggested that plasma membrane sphingolipids and
cholesterol spontaneously coalesce into raft-like microdomains and that
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specific proteins, including CD4 and some other T-cell signaling molecules, sequester into these rafts. In agreement with these results, we found that CD4 and the associated Lck tyrosine kinase of peripheral blood mononuclear cells and H9 leukemic T cells were selectively and highly enriched in a low-density lipid fraction that was resistant at 0 degrees C to the neutral detergent Triton X-100 but was disrupted by extraction of cholesterol with filipin or methyl-beta-cyclodextrin. In contrast, the CXCR4 chemokine receptor, a coreceptor for X4 strains of human immunodeficiency virus type 1 (HIV -1), was almost completely excluded from the detergent-resistant raft fraction. Accordingly, as determined by immunofluorescence with confocal microscopy, CD4 and CXCR4 did not coaggregate into antibody-induced cell surface patches or into patches of CXCR4 that formed naturally at the ruffled edges of adherent cells. The CXCR4 fluorescent patches were extracted with cold 1% Triton X-100, whereas the CD4 patches were resistant. In stringent support of these data, CD4 colocalized with patches of cholera toxin bound to the raft-associated sphingoglycolipid GM1 , whereas CXCR4 did not. Addition of the CXCR4-activating chemokine SDF-1 alpha did not induce CXCR4 movement into rafts. Moreover, binding of purified monomeric gp120 envelope glycoproteins from strains of HIV -1 that use this coreceptor did not stimulate detectable redistributions of CD4 or CXCR4 between their separate membrane domains. However, adsorption of multivalent gp120-containing HIV -1 virion particles appeared to destabilize the local CD4-containing rafts. Indeed, adsorbed HIV -1 virions were detected by immunofluorescence microscopy and were almost all situated in nonraft regions of the cell surface. We conclude that HIV -1 initially binds to CD4 in a raft domain and that its secondary associations with CXCR4 require shifts of proteins and associated lipids away from their preferred lipid microenvironments. Our evidence suggests that these changes in protein-lipid interactions destabilize the plasma membrane microenvironment underlying the virus by at least several kilocalories per mole, and we propose that this makes an important contribution to fusion of the viral and cellular membranes during infection. Thus, binding of HIV -1 may be favored by the presence of CD4 in rafts, but the rafts may then disperse prior to the membrane fusion reaction.

4/AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10772721 20016510 PMID: 10547418
Formulation of HIV -envelope protein with lipid vesicles expressing ganglioside GM1 associated to cholera toxin B enhances mucosal immune responses.
Lian T; Bui T; Ho RJ
Department of Pharmaceutics, School of Pharmacy, University of Washington, Box 357610, H272 Health Sciences Building, Seattle, WA 98195-7610, USA.
Vaccine (ENGLAND) Nov 12 1999, 18 (7-8) p604-11, ISSN 0264-410X
Journal Code: X60
Contract/Grant No.: AI31854, AI, NIAID; HL56548, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Taking advantage of the ability of pentameric cholera toxin B subunit (CTB) to bind selectively to GM1 , we developed recently a CTB-mediated GM1 lipid vesicle delivery system to target drugs and proteins to mucosal tissues [1]. In this report, we present the use of such a strategy to deliver an HIV envelope protein (HIV -env) to mucosal tissues via intranasal route. Intranasal administration of a recombinant HIV envelope protein formulated in CTB-associated GM1 lipid vesicles enhanced mucosal IgA antibody responses detected in the nasal and gut tissues, compared to

that of control animals immunized with antigen formulated in GM1 -free vesicles with CTB or formulated in alum-associated vesicles with CTB. We found a nearly 2- to 3-fold enhancement in IgA antibody titers detected both in nasal and gut tissues using the CTB- GM1 lipid vesicle delivery system, compared to using the GM1 -free lipid vesicle system. Intranasal administration of HIV -env formulated in the CTB-associated GM1 vesicles also induced a significant level of serum IgG and cellular immune responses against HIV -env. IgG isotype analysis indicates that CTB in GM1 vesicle delivery system enhanced both IgG1 and IgG2a while CTB in alum formulation enhanced only IgG1. However, IgA and IgG antibody responses against CTB were similar for GM1 vesicles regardless of whether HIV -env was present in the vaccine formulation. Collectively, these data indicate that delivery of HIV -env to mucosal epithelial cells with CTB-associated GM1 lipid vesicles enhanced mucosal and systemic immune responses against the HIV -envelope protein. It is possible that both the CTB-mediated targeted delivery of antigen-loaded GM1 lipid vesicles and mucosal adjuvanticity of CTB may be involved in enhancing the immune responses.

4/AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10064696 99128419 PMID: 9927761
Human milk glycoconjugates that inhibit pathogens.
Newburg DS
Shriver Center for Mental Retardation 200 Trapelo Road, Waltham, Massachusetts 02452 USA.
Current medicinal chemistry (NETHERLANDS) Feb 1999, 6 (2) p117-27, ISSN 0929-8673 Journal Code: C02
Languages: ENGLISH
Document type: Journal Article; Review; Review, Tutorial
Record type: Completed
Breast-fed infants have lower incidence of diarrhea, respiratory disease, and otitis media. The protection by human milk has long been attributed to the presence of secretory IgA. However, human milk contains large numbers and amounts of complex carbohydrates, including glycoproteins, glycolipids, glycosaminoglycans, mucins, and especially oligosaccharides. The oligosaccharides comprise the third most abundant solid constituent of human milk, and contain a myriad of structures. Complex carbohydrate moieties of glycoconjugates and oligosaccharides are synthesized by the many glycosyltransferases in the mammary gland; those with homology to cell surface glycoconjugate pathogen receptors may inhibit pathogen binding, thereby protecting the nursing infant. Several examples are reviewed: A fucosyloligosaccharide inhibits the diarrheagenic effect of stable toxin of Escherichia coli. A different fucosyloligosaccharide inhibits infection by Campylobacter jejuni. Binding of Streptococcus pneumoniae and of enteropathogenic E. coli to their respective receptors is inhibited by human milk oligosaccharides. The 46-kD glycoprotein, lactadherin, inhibits rotavirus binding and infectivity. Low levels of lactadherin in human milk are associated with a higher incidence of symptomatic rotavirus in breast-fed infants. A mannosylated glycopeptide inhibits binding by enterohemorrhagic E. coli. A glycosaminoglycan inhibits binding of gp120 to CD4, the first step in HIV infection. Human milk mucin inhibits binding by S-fimbriated E. coli. The ganglioside, GM1 , reduces diarrhea production by cholera toxin and labile toxin of E. coli. The neutral glycosphingolipid, Gb3 , binds to Shigatoxin. Thus, many complex carbohydrates of human milk may be novel antipathogenic agents, and the milk glycoconjugates and oligosaccharides may be a major source of protection for breastfeeding infants.

4/AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08878917 96238945 PMID: 8648123
Mycobacterium avium- and Mycobacterium tuberculosis -containing vacuoles are dynamic, fusion-competent vesicles that are accessible to glycosphingolipids from the host cell plasmalemma.
Russell DG; Dant J; Sturgill-Koszycki S
Department of Molecular Microbiology, Washington University School of Medicine, St. Louis, MO 63310, USA.
Journal of immunology (UNITED STATES) Jun 15 1996, 156 (12) p4764-73
, ISSN 0022-1767 Journal Code: IFB
Contract/Grant No.: AI 33348, AI, NIAID; HL 55936, HL, NHLBI
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The vacuoles inhabited by viable Mycobacterium avium and Mycobacterium tuberculosis show limited fusion with endosomal and lysosomal compartments. This ability to regulate the maturation of their phagosomal compartments and restrict their differentiation into hydrolytically active vacuoles appears to correlate with the survival of the bacilli. Data presented in this current study demonstrate that despite the apparent isolation of mycobacterial vacuoles from the lysosomal network, they are dynamic, fusion-competent vesicles. Exploiting the ability of cholera toxin B subunit to bind to GM1 ganglioside on the macrophage plasmalemma, we demonstrate that these glycosphingolipids have ready access to the mycobacterial vacuoles. Entry into mycobacterial vacuoles is rapid, within 5 min of addition to the cells, and does not proceed through a brefeldin A-sensitive pathway. Furthermore, the gangliosides follow a route that differs from that taken by fluid-phase markers. TLC analysis gangliosides isolated from Mycobacterium -containing vacuoles, and IgG-bead phagosomes reveal similar profiles. These data indicate that rather than being fusion incompetent, mycobacterial vacuoles are actually highly dynamic, fusion-competent vesicles that behave like an extension of the recycling endosomal apparatus.

4/AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08857245 94282916 PMID: 8013109
ELISA-type titertray assay of IgM anti- GM1 autoantibodies.
Bech E; Jakobsen J; Orntoft TF
Department of Clinical Chemistry, Aarhus University Hospital, Denmark.
Clinical chemistry (UNITED STATES) Jul 1994, 40 (7 Pt 1) p1331-4,
ISSN 0009-9147 Journal Code: DBZ
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We report an ELISA-type titertray assay for autoantibodies against the ganglioside GM1 . Trays were coated with ganglioside GM1 and reacted with patients' sera; bound IgM was detected with rabbit antibody to human IgM. High-titer serum from a patient was used as calibrator, another patient's serum as the positive control, and the GM1 -specific cholera toxin as the control for GM1 coating. Regression curves of serum titers obtained from different patients were linear and parallel. Intra- and interassay CVs were 4.0-7.8% and 5.5-16%, respectively. We detected antibodies at a titer of 1:250 in normal subjects. Analytical specificity of the calibrator serum against GM1 was demonstrated by immune thin-layer chromatography. Anti- GM1 antibodies were increased in patients with chronic inflammatory demyelinating polyradiculoneuropathy ($P < 0.002$) or

multiple sclerosis (P < 0.01). In Guillain-Barre syndrome, preliminary longitudinal studies showed a decrease in anti- GM1 titer that was related to clinical recovery.

4/AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08675927 96096516 PMID: 8522171
Characterization of an internal permissive site in the cholera toxin B-subunit and insertion of epitopes from human immunodeficiency virus-1, hepatitis B virus and enterotoxigenic Escherichia coli.
Bckstrom M; Holmgren J; Schodel F; Lebens M
Department of Medical Microbiology and Immunology, Goteborg University, Sweden.
Gene (NETHERLANDS) Nov 20 1995, 165 (2) p163-71, ISSN 0378-1119
Journal Code: FOP
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
We previously described the construction of novel hybrid proteins based on the B-subunit of cholera toxin (CTB) [Backstrom et al., Gene 149 (1994) 211-217], in which a neutralizing B-cell epitope from the third variable (V3) loop in the envelope glycoprotein gp120 from human immunodeficiency virus type 1 (HIV -1) was inserted within a surface-exposed region between amino acids (aa) 55 and 64. The resulting protein retained properties of native CTB and could induce strong anti-CTB antibody (Ab) responses, but the inserted gp120 epitope was only modestly immunogenic. In this study, the potential use of this internal permissive site in CTB for the insertion of heterologous epitopes has been further investigated. Six additional plasmids were constructed encoding HIV ::CTB hybrid proteins with ten to fourteen aa from the V3 loop of gp120 genetically inserted at different positions between aa 52 and 65, with deletions of different CTB aa. Plasmids encoding proteins with peptides inserted between aa 53 and 64 in CTB gave rise to stable proteins which reacted with CTB-specific monoclonal antibodies (mAb) and bound to GM1 gangliosides (GM1), indicating that insertions between these positions do not drastically alter the conformation or the receptor-binding properties of native CTB. Plasmids were also constructed encoding CTB hybrid proteins which had either an 11-aa peptide from hepatitis B virus (HBV) pre-S(2) or one of two peptides related to the heat-stable toxin (STa) of enterotoxigenic Escherichia coli inserted between aa 55 and 64 of CTB. This resulted in the production of HBV::CTB or ST::CTB hybrid proteins and illustrated that the internal permissive site can be used for insertion of peptides of varying aa composition. The reactivity of the inserted epitopes with epitope-specific mAb in GM1 -ELISA and immunoblots varied greatly between hybrid proteins and depended on the position in CTB and the aa composition of the inserted peptides. Despite these differences, all the HIV ::CTB, ST::CTB and HBV::CTB hybrid proteins could induce low, but significant, levels of serum Ab in mice against gp120, STa or pre-S(2), in addition to strong serum Ab responses against CTB. The Ab response against the internally inserted gp120 peptide was similar to that against the same peptide fused to the N-terminus of CTB, indicating that internally placed peptides had similar immunogenicity to the same peptides added terminally.

4/AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08658866 96021579 PMID: 7483767
Gene fusion of cholera toxin B subunit and HBV PreS2 epitope and the

antigenicity of fusion protein.
Shi CH; Cao C; Xhig JS; Li J; Ma QJ
Molecular Genetics Center, Institute of Biotechnology, Beijing, Republic of China.
Vaccine (ENGLAND) Jul 1995, 13 (10) p933-7, ISSN 0264-410X
Journal Code: X6O
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
A unique EcoRI site was introduced at the 3' end of cholera toxin B subunit (CTB) gene by site-directed mutagenesis, polynucleotides encoding 120-145aa epitope of HBV PreS2 were chemically synthesized and fused to the 3' end of cholera toxin B subunit gene. The fused gene was over-expressed (about 30 micrograms ml-1) in E. coli, and more than 95% of the fusion protein was secreted into the medium. The fusion protein expressed was purified by affinity chromatography. The chimera protein obtained bound to ganglioside GM1 , and had the antigenicity of both cholera toxin B subunit and HBV PreS2 as confirmed by ELISA. After mice were immunized intramuscularly with the fusion protein, anti-CTB antibody and anti-PreS2 antibody were produced. These results indicated that the fusion protein retained not only the biological function of CTB but also the antigenicity and the immunogenicity of cholera toxin B subunit and HBV PreS2 epitope. This work provided a sound basis for further studies on the construction of engineered peptide vaccine.

4/AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08382422 95047479 PMID: 7525413
Insertion of a HIV -1-neutralizing epitope in a surface-exposed internal region of the cholera toxin B-subunit.
Backstrom M; Lebens M; Schodel F; Holmgren J
Department of Medical Microbiology and Immunology, University of Goteborg, Sweden.
Gene (NETHERLANDS) Nov 18 1994, 149 (2) p211-7, ISSN 0378-1119
Journal Code: FOP
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
The non-toxic B-subunit of cholera toxin (CTB) is a powerful immunogen and has been investigated as a carrier for foreign peptide epitopes, with peptides genetically fused to either the N- or C terminus of CTB. In the present study, we have constructed a plasmid encoding a novel intrachain CTB fusion protein with a peptide epitope inserted into an internal region of CTB: eight amino acids (aa) in CTB (56-63) were substituted with a 10-aa peptide from the third variable (V3) loop of the HIV -1 envelope protein gp120. The resulting chimeric protein retained important functional characteristics of the native CTB including pentamerization and GM1 ganglioside receptor binding. The internal hybrid protein was also shown to be resistant to proteolytic degradation during production in Vibrio cholerae, whereas a terminal hybrid protein, where the same gp120-epitope was fused to the N terminus of CTB, was rapidly cleaved during culture. The inserted epitope, which is known to give rise to HIV -1 neutralizing Ab, could be detected with a V3 loop-specific monoclonal Ab when the chimeric protein was analyzed in ELISA and immunoblot, indicating that the epitope inserted at this site is presented on the surface of the protein. Consistent with these observations, immunization of mice with the CTB:: HIV hybrid protein elicited a high titered serum Ab response to the CTB moiety and also, in some but not all animals, a detectable response to the inserted gp120

epitope.

4/AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08240655 94377479 PMID: 8090758
Specific inhibition of herpes virus replication by receptor-mediated entry of an antiviral peptide linked to Escherichia coli enterotoxin B subunit.
Marcello A; Loregian A; Cross A; Marsden H; Hirst TR; Palu G
Institute of Microbiology, University of Padova, Italy.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Sep 13 1994, 91 (19) p8994-8, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Mimetic peptides capable of selectively disrupting protein-protein interactions represent potential therapeutic agents for inhibition of viral and cellular enzymes. This approach was first suggested by the observation that the peptide YAGAVVNDL, corresponding to the carboxyl-terminal 9 amino acids of the small subunit of ribonucleotide reductase of herpes simplex virus, specifically inhibited the viral enzyme in vitro. Evaluation and use of this peptide as a potential antiviral agent has, however, been thwarted by its failure to inhibit virus replication in vivo, presumably because the peptide is too large to enter eukaryotic cells unaided. Here, we show that the nontoxic B subunit of Escherichia coli heat-labile enterotoxin can be used as a recombinant carrier for the receptor-mediated delivery of YAGAVVNDL into virally infected cells. The resultant fusion protein specifically inhibited herpes simplex virus type 1 replication and ribonucleotide reductase activity in quiescent Vero cells. Preincubation of the fusion protein with soluble GM1 ganglioside abolished this antiviral effect, indicating that receptor-mediated binding to the target cell is necessary for its activity. This provides direct evidence of the usefulness of carrier-mediated delivery to evaluate the intracellular efficacy of a putative antiviral peptide.

4/AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07752260 93019059 PMID: 1383408
Vaccination by cholera toxin conjugated to a herpes simplex virus type 2 glycoprotein D peptide.
Drew MD; Estrada-Correa A; Underdown BJ; McDermott MR
Department of Pathology, McMaster University, Hamilton, Ontario, Canada.
Journal of general virology (ENGLAND) Sep 1992, 73 (Pt 9) p2357-66, ISSN 0022-1317 Journal Code: I9B
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
Immunization of BALB/cJ mice with a peptide corresponding to residues 1 to 23 of glycoprotein D [gD(1-23)] from herpes simplex virus type 2 (HSV -2) elicits antibody responses which correlate with protection against lethal HSV -2 infection. In the present study, we examined the ability of cholera toxin (CTX) to act as an immunogenic carrier for gD(1-23). The number of gD(1-23) residues conjugated to CTX affected its binding to GM1 ganglioside and physiological toxicity, both of which are factors affecting oral immunogenicity. The antibody response elicited after intraperitoneal (i.p.) immunization with the CTX-gD(1-23) conjugate was

protective against a lethal i.p. challenge with HSV -2. In other experiments, mice were immunized i.p. on day 0 and subsequent immunizations conducted on days 14 and 28 were administered either intragastrically or intravaginally (i.vag.). Intraperitoneal priming followed by either i.p or intragastric boosting resulted in anti- HSV -2 antibodies in vaginal washings and in protection against a lethal i.vag. challenge with HSV -2. Intraperitoneal priming followed by i.vag. boosting did not elicit anti- HSV -2 antibodies in vaginal washings and did not protect mice against a lethal i.vag. challenge with HSV -2. These results suggest that CTX can act as a systemic and an oral delivery molecule for the covalently linked gD(1-23) peptide and that such conjugates can elicit protective immune responses against systemic and genital HSV -2 infection.

4/AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07073985 93266307 PMID: 8388365
Intranasal immunization against herpes simplex virus infection by using a recombinant glycoprotein D fused with immunomodulating proteins, the B subunit of Escherichia coli heat-labile enterotoxin and interleukin-2.
Hazama M; Mayumi-Aono A; Miyazaki T; Hinuma S; Fujisawa Y
Biology Research Laboratory, Takeda Chemical Industries, Ltd., Osaka, Japan.
Immunology (ENGLAND) Apr 1993, 78 (4) p643-9, ISSN 0019-2805
Journal Code: GH7
Languages: ENGLISH
Document type: Journal Article
Record type: Completed
To establish a novel strategy of mucosal immunization against herpes simplex virus type 1 (HSV -1) infection, we studied the immune responses elicited by intranasal immunization with several forms of a recombinant glycoprotein D (gD) of HSV -1. A truncated gD (t-gD) co-administered with heat-labile enterotoxin B subunit (LTB) from Escherichia coli induced both a mucosal immune response involving secretion of anti-gD IgA and serum IgG production. The levels of these responses are comparable to those in mice which have recovered from intranasal HSV -1 infections. The fusion protein (t-gD-LTB), consisting of t-gD and LTB, induced the responses more efficiently than did co-administration of t-gD and LTB, although GM1 ganglioside binding activity was significantly reduced in t-gD-LTB. We found that another fusion protein, consisting of t-gD and human interleukin-2 (t-gD-IL-2), also elicited antibody responses comparable to those induced by t-gD-LTB. Immunity acquired by intranasal immunization with t-gD-IL-2 protected mice from intraperitoneal HSV -1 infections, whereas t-gD-LTB or t-gD alone failed to provide protection against infection. Even in a mouse strain that responded highly to subcutaneously administered gD, intranasally administered t-gD did not elicit antibody responses. The lack of response to gD was clearly abrogated by co-administration with IL-2, and administration of t-gD-IL-2 induced an excellent level of antibody responses in this strain. These results suggest that the IL-2 fusion strategy yields a new type of mucosal immunization, the mechanism of which differs from that speculated for the mucosal adjuvant activity of LTB.

4/AB/12 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

10109195 Genuine Article#: 485BR Number of References: 60

Title: Legionella pneumophila is internalized by a macropinocytotic uptake pathway controlled by the Dot/Icm system and the mouse Lgn1 locus (ABSTRACT AVAILABLE)
Author(s): Watarai M; Derre I; Kirby J; Growney JD; Dietrich WF; Isberg RR (REPRINT)
Corporate Source: Tufts Univ,Sch Med, Dept Mol Biol & Microbiol,136 Harrison Ave/Boston//MA/02111 (REPRINT); Tufts Univ,Sch Med, Dept Mol Biol & Microbiol,Boston//MA/02111; Tufts Univ,Sch Med, Howard Hughes Med Inst,Boston//MA/02111; Harvard Univ,Sch Med, Dept Genet,Boston//MA/02115
Journal: JOURNAL OF EXPERIMENTAL MEDICINE, 2001, V194, N8 (OCT 15), P 1081-1095
ISSN: 0022-1007 Publication date: 20011015
Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021 USA
Language: English Document Type: ARTICLE
Abstract: The products of the Legionella pneumophila dot/icm genes enable the bacterium to replicate within a macrophage vacuole. This study demonstrates that the Dot/Icm machinery promotes macropinocytotic uptake of L. pneumophila into mouse macrophages. In mouse strains harboring a permissive Lgn1 allele, L. pneumophila promoted formation of vacuoles that were morphologically similar to macropinosomes and dependent on the presence of an intact Dot/ Icm system. Macropinosome formation appeared to occur during, rather than after, the closure of the plasma membrane about the bacterium, since a fluid-phase marker preloaded into the macrophage endocytic path failed to label the bacterium-laden macropinosome. The resulting macropinosomes were rich in GM1 gangliosides and glycosylphosphatidylinositol-linked proteins. The Lgn1 allele restrictive for L. pneumophila intracellular replication prevented dot/icm-dependent macropinocytosis, with the result that phagosomes bearing the microorganism were targeted into the endocytic network. Analysis of macrophages from recombinant inbred mouse strains support the model that macropinocytotic uptake is controlled by the Lgn1 locus. These results indicate that the products of the dot/icm genes and Lgn1 are involved in controlling an internalization route initiated at the time of bacterial contact with the plasma membrane.

4/AB/13 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07187186 Genuine Article#: 134BK Number of References: 39
Title: Cholera toxin stimulates type II pneumocyte proliferation by a cyclic AMP-independent mechanism (ABSTRACT AVAILABLE)
Author(s): Uhal BD (REPRINT) ; Papp M; Flynn K; Steck ME
Corporate Source: MICHAEL REESE HOSP & MED CTR,CARDIOVASC INST, LUNG CELL KINET LAB, 2929 S ELLIS AVE, RM 405KND/CHICAGO//IL/60616 (REPRINT); PENN STATE UNIV,MILTON S HERSHEY MED CTR, DEPT CELLULAR & MOL PHYSIOL/HERSHEY//PA/17033
Journal: BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH, 1998, V1405 , N1-3 (OCT 21), P99-109
ISSN: 0167-4889 Publication date: 19981021
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: Cholera toxin (CT) stimulated DNA synthesis by low-density primary cultures of adult rat type II pneumocytes (T2P) in a dose-dependent manner, either in the presence or the absence of serum. In the presence of 1% rat serum, 1 mu g/ml CT also stimulated a 50% increase in cell number over 8 days of incubation ($P < 0.01$); this was

in addition to a 2-fold increase in cell number induced by the serum alone ($P < 0.05$). The same dose of CT also elevated intracellular cAMP and the total activity of protein kinase A (both $P < 0.01$), suggesting toxin stimulation of T2P proliferation by a cAMP-dependent mechanism. However, the effect of CT on DNA synthesis could not be mimicked by 8-bromoadenosine 3':5'-cyclic monophosphate (8-bromo-cAMP), nor by N-6,2'-O-dibutyryladenosine 3':5'-cyclic monophosphate (dibutyryl-cAMP), each tested over a wide range of concentrations. L-Isoproterenol stimulated surfactant secretion by over 5-fold ($P < 0.01$), but neither the P-agonist, forskolin nor 3-isobutyl-1-methylxanthine had any significant effect on DNA synthesis. The purified B-subunit of CT stimulated DNA synthesis to the same degree as did the holotoxin, either in the presence or the absence of rat serum. In contrast, the purified A-subunit had no significant effect. These data suggest that cholera toxin stimulates type II pneumocyte proliferation through a mechanism that is independent of cAMP, protein kinase A and toxin-catalyzed ADP-ribosylation.

4/AB/14 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

05705509 Genuine Article#: WR325 Number of References: 49
Title: Neutral glycosphingolipids and gangliosides from spleen T lymphoblasts of genetically different inbred mouse strains (ABSTRACT AVAILABLE)
Author(s): Muthing J (REPRINT)
Corporate Source: UNIV BIELEFELD,INST CELL CULTURE TECHNOL/D-33501 BIELEFELD//GERMANY/ (REPRINT)
Journal: GLYCOCONJUGATE JOURNAL, 1997, V14, N2 (FEB), P241-248
ISSN: 0282-0080 Publication date: 19970200
Publisher: CHAPMAN HALL LTD, 2-6 BOUNDARY ROW, LONDON, ENGLAND SE1 8HN
Language: English Document Type: ARTICLE
Abstract: The gangliosides G(M1b), GalNAc-G(M1b), and G(D1 alpha), are typical compounds of concanavalin A stimulated splenic T lymphoblasts of CBA/J inbred mice. Their structural characterization has been described in previous studies. The intention of this work was the comparative TLC immunostaining analysis of the glycosphingolipid composition of lectin stimulated splenic T lymphoblasts obtained from six genetically different inbred mouse strains. The strains examined were AKR, BALB/c, C57BL/6, CBA/J, DBA/2 and WHT/Ht, which are commonly used for biochemical and immunological studies. The neutral glycosphingolipid GgOse(4)Cer, the precursor for G(M1b)-type gangliosides, was expressed by all six strains investigated. AKR, C57BL/6 and DBA/2 showed high and BALB/c, CBA/J and WHT/Ht diminished expression in T lymphoblasts, based on single cell calculation. The gangliosides G(M1b) and GalNAc-G(M1b), elongation products of GgOse(4)Cer, displayed strain-specific differences in their intensities, which were found to correlate with the intensities of GgOse(4)Cer expression of the same strains. Concerning sialic acid substitution of gangliosides, G(M1b) and GalNAc-G(M1b), predominantly carry N-acetylneuraminic acid, whereas choleragenoid receptors G(M1a), and Gal-GalNAc-G(M1b), which are also expressed by all six strains, are characterized by dominance of N-glycolylneuraminic acid. Two highly polar gangliosides, designated with X and Y, which have not been previously recognized in murine lymphoid tissue, were detected by positive anti-GalNAc-G(M1b) antibody and choleragenoid binding, respectively. Both gangliosides were restricted to AKR, DBA12 and C57BL/6 mice. The other three strains BALB/c, CBA/J and WHT/Ht are

lacking these structures. In summary, the G(M1b)-type pathway is quite active in all six strains analysed in this study. Strain-specific genetic variations in T lymphoblast gangliosides were observed with the occurrence of gangliosides X and Y. This study and data from other groups strongly indicate for G(M1b)-type gangliosides a functional association with T cell activation and leukocyte mediated reactions.

4/AB/15 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04876379 Genuine Article#: UP662 Number of References: 40
Title: MYCOBACTERIUM -AVIUM-CONTAINING AND MYCOBACTERIUM - TUBERCULOSIS -CONTAINING VACUOLES ARE DYNAMIC, FUSION-COMPETENT VESICLES THAT ARE ACCESSIBLE TO GLYCOSPHINGOLIPIDS FROM THE HOST-CELL PLASMALEMMA (Abstract Available)
Author(s): RUSSELL DG; DANT J; STURGILLKOSZYCKI S
Corporate Source: WASHINGTON UNIV,SCH MED,DEPT MOLEC MICROBIOL,660 S EUCLID AVE/ST LOUIS//MO/63110
Journal: JOURNAL OF IMMUNOLOGY, 1996, V156, N12 (JUN 15), P4764-4773
ISSN: 0022-1767
Language: ENGLISH Document Type: ARTICLE
Abstract: The vacuoles inhabited by viable Mycobacterium avium and Mycobacterium tuberculosis show limited fusion with endosomal and lysosomal compartments. This ability to regulate the maturation of their phagosomal compartments and restrict their differentiation into hydrolytically active vacuoles appears to correlate with the survival of the bacilli, Data presented in this current study demonstrate that despite the apparent isolation of mycobacterial vacuoles from the lysosomal network, they are dynamic, fusion-competent vesicles. Exploiting the ability of cholera toxin B subunit to bind to GM1 ganglioside on the macrophage plasmalemma, we demonstrate that these glycosphingolipids have ready access to the mycobacterial vacuoles. Entry into mycobacterial vacuoles is rapid, within 5 min of addition to the cells, and does not proceed through a brefeldin A-sensitive pathway. Furthermore, the gangliosides follow a route that differs from that taken by fluid-phase markers, TLC analysis of gangliosides isolated from Mycobacterium -containing vacuoles, and IgG-bead phagosomes reveal similar profiles. These data indicate that rather than being fusion incompetent, mycobacterial vacuoles are actually highly dynamic, fusion-competent vesicles that behave like an extension of the recycling endosomal apparatus.

4/AB/16 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03384229 Genuine Article#: PB373 Number of References: 59
Title: THE GANGLIOSIDE G(D1-ALPHA),IV(3)NEU5AC,III(6)NEU5AC-GGOSE(4)CER, IS A MAJOR DISIALOGANGLIOSIDE IN THE HIGHLY METASTATIC MURINE LYMPHORETICULAR TUMOR-CELL LINE MDAY-D2 (Abstract Available)
Author(s): MUTHING J; PETERKATALINIC J; HANISCH FG; UNLAND F; LEHMANN J
Corporate Source: UNIV BIELEFELD,INST ZELLKULTURTECH,POSTFACH 100131/D-33501 BIELEFELD//GERMANY/; UNIV BONN,INST PHYSIOL CHEM/D-53115 BONN//GERMANY/; UNIV COLOGNE,INST IMMUNBIOL/D-50937 COLOGNE//GERMANY/
Journal: GLYCOCONJUGATE JOURNAL, 1994, V11, N2 (APR), P153-162
ISSN: 0282-0080
Language: ENGLISH Document Type: ARTICLE
Abstract: The aim of the present study was to investigate the ganglioside

expression of the highly metastatic murine lymphoreticular tumour cell line MDAY-D2. Cells were propagated under controlled pH conditions and oxygen supply in bioreactors of 1 and 7.51 volumes by repeated batch fermentation. Gangliosides were isolated from 2.7 x 10(11) cells, purified by silica gel chromatography and separated into mono- and disialoganglioside fractions by preparative DEAE anion exchange high performance liquid chromatography. Individual gangliosides were obtained by preparative thin layer chromatography. Their structural features were established by immunostaining, fast atom bombardment and gas chromatography mass spectrometry. In addition to gangliosides of the G(M1a)-pathway (G(M)2, G(M1a) and G(D1a)) and G(M1b) (IV(3)Neu5Ac-GgOse(4)Cer) and GalNAc-G(M1b) of the G(M16)-pathway, the disialoganglioside G(D1a) (IV(3)Neu5Ac, III(6)Neu5Ac-GgOse(4)Cer) was found in equal amounts compared to G(D1a) (IV(3)Neu5Ac,II(3)Neu5Ac-GgOse(4)Cer). All gangliosides were substituted with C-24:0,C-24:1 and C-16:0 fatty acids, sphingosine and N-acetylneuraminic acid as the sole sialic acid.

4/AB/17 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03198584 Genuine Article#: BA19K Number of References: 49
Title: GANGLIOSIDES AS MODULATORS OF NEURONAL CALCIUM
Author(s): WU GS; LEDEEN RW
Corporate Source: UNIV MED & DENT NEW JERSEY,NEW JERSEY MED SCH,DEPT NEUROSCI,185 S ORANGE AVE/NEWARK//NJ/07103; UNIV MED & DENT NEW JERSEY,NEW JERSEY MED SCH,DEPT PHYSIOL/NEWARK//NJ/07103
Journal: PROGRESS IN BRAIN RESEARCH, 1994, V101, P101-112
ISSN: 0079-6123
Language: ENGLISH Document Type: REVIEW

4/AB/18 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03038798 Genuine Article#: MY529 Number of References: 40
Title: IN-VITRO MODULATION OF CHANGES IN GANGLIOSIDE PATTERNS OF DIFFERENTIATING NEURONS IN THE PRESENCE OF AN ANTI- GM1 ANTIBODY (Abstract Available)
Author(s): ALLENDE ML; PANZETTA P
Corporate Source: UNIV NACL CORDOBA,FAC CIENCIAS QUIM,DEPT QUIM BIOL,CC 61/RA-5016 CORDOBA/CORDOBA/ARGENTINA/; UNIV NACL CORDOBA,FAC CIENCIAS QUIM,DEPT QUIM BIOL/RA-5016 CORDOBA/CORDOBA/ARGENTINA/; CONSEJO NACL INVEST CIENT & TECN,CIQUIBIC/CORDOBA/CORDOBA/ARGENTINA/
Journal: JOURNAL OF NEUROSCIENCE RESEARCH, 1994, V37, N4 (MAR 1), P497-505
ISSN: 0360-4012
Language: ENGLISH Document Type: ARTICLE
Abstract: Retinal cells from 7-day-old chicken embryos were cultured in the presence of a polyclonal anti- GM1 antibody, at low and high density in a ''sandwich cell culture''. Cells that were about 80% neurofilament positive at all times, changed their morphology and emitted processes as controls. By examining immunocytochemical expression of gangliosides, cells cultured in the presence of the antibody maintained GD3 expression longer than controls, albeit the expression of the gangliotetraosylgangliosides (GTOG) was not considerably affected. This leads to an extension of the transient period in which differentiating cells coexpressed both types of gangliosides (GD3 and GTOG). At 3-4 days in vitro the relative synthesis of GD3 was about 30% higher and

that of GD1a about 40% lower than in controls, indicating a delay in the shift of the synthesis pattern. Nevertheless, the pattern of ganglioside composition resembled at 4 days in vitro.

4/AB/19 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02985942 Genuine Article#: MU871 Number of References: 48
Title: DIFFERENT DISTRIBUTIONS OF GLYCOSPHINGOLIPIDS IN MOUSE AND RABBIT SKELETAL-MUSCLE DEMONSTRATED BY BIOCHEMICAL AND IMMUNOHISTOLOGICAL ANALYSES (Abstract Available)
Author(s): MUTHING J; MAURER U; SOSTARIC K; NEUMANN U; BRANDT H; DUVAR S; PETERKATALINIC J; WEBERSCHURHOLZ S
Corporate Source: UNIV BIELEFELD,FAK TECH,ARBEITGRP ZELLKULTURTECH,POSTFACH 100131/D-33501 BIELEFELD//GERMANY/; UNIV BIELEFELD,INST CELL CULTURE TECHNOL/BIELEFELD//GERMANY/; UNIV ZAGREB,SCH MED,DEPT CHEM & BIOCHEM/ZAGREB//CROATIA/; HANNOVER SCH VET MED,POULTRY CLIN/HANNOVER//GERMANY/; UNIV BONN,INST PHYSIOL CHEM/W-5300 BONN//GERMANY/; UNIV BIELEFELD,INST DEV BIOL/BIELEFELD//GERMANY/
Journal: JOURNAL OF BIOCHEMISTRY, 1994, V115, N2 (FEB), P248-256
ISSN: 0021-924X
Language: ENGLISH Document Type: ARTICLE
Abstract: The expression of neutral glycosphingolipids and gangliosides was investigated in mouse and rabbit skeletal muscle by means of biochemical and immunochemical techniques. Neutral glycosphingolipids from muscle of the inbred rabbit strain used in this study showed a simple TLC pattern, comprising mainly monohexosylceramide. In addition to this compound, lactosylceramide, lacto-N-neotetraosylceramide, globoside and Forssman GSL were detected in mouse muscle. The major ganglioside in both species was G(M3); G(M3)(Neu5Ac) and G(M3)(Neu5Gc) were found in a 3 : 1 ratio in mouse muscle, whereas the absence of G(M3)(Neu5Gc) is characteristic of rabbit muscle. As a general structural feature of all muscle G(M3) gangliosides investigated, a C-18 fatty acid and C-18 sphingosine were the major components besides minor C-22 and C-24 : 1 fatty acids of the respective ceramide portions, as revealed by positive and negative ion FAB-MS. alpha 2-3 sialylated lacto-N-neotetraosylceramide (sialylparagloboside) was expressed in both species, whereas the alpha 2-6 sialylated isomeric compound was found only in mouse muscle. Minute quantities of ganglio-series G(M1), G(D1a), G(D1b), and G(T1b) Were detected in muscles from both species. Glycosphingolipid expression could be con firmed immunohistochemically by examining transverse and longitudinal cryosections of skeletal muscle samples. The results provide the basis for the investigation of muscle specific glycosphingolipids that might modulate membrane protein functions in muscle.

4/AB/20 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02354890 Genuine Article#: KV869 Number of References: 33
Title: INTRANASAL IMMUNIZATION AGAINST HERPES -SIMPLEX VIRUS-INFECTION BY USING A RECOMBINANT GLYCOPROTEIN-D FUSED WITH IMMUNOMODULATING PROTEINS, THE B-SUBUNIT OF ESCHERICHIA - COLI HEAT-LABILE ENTEROTOXIN AND INTERLEUKIN-2 (Abstract Available)
Author(s): HAZAMA M; MAYUMIAONO A; MIYAZAKI T; HINUMA S; FUJISAWA Y
Corporate Source: TAKEDA CHEM IND LTD,DIV PHARMACEUT RES,BIOL RESLAB/OSAKA 532//JAPAN/

Journal: IMMUNOLOGY, 1993, V78, N4 (APR), P643-649
ISSN: 0019-2805
Language: ENGLISH Document Type: ARTICLE
Abstract: To establish a novel strategy of mucosal immunization against herpes simplex virus type 1 (HSV -1) infection, we studied the immune responses elicited by intranasal immunization with several forms of a recombinant glycoprotein D (gD) of HSV -1. A truncated gD (t-gD) co-administered with heat-labile enterotoxin B subunit (LTB) from Escherichia coli induced both a mucosal immune response involving secretion of anti-gD IgA and serum IgG production. The levels of these responses are comparable to those in mice which have recovered from intranasal HSV -1 infections. The fusion protein (t-gD-LTB), consisting of t-gD and LTB, induced the responses more efficiently than did co-administration of t-gD and LTB, although GM1 ganglioside binding activity was significantly reduced in t-gD-LTB. We found that another fusion protein, consisting of t-gD and human interleukin-2 (t-gD-IL-2), also elicited antibody responses comparable to those induced by t-gD-LTB. Immunity acquired by intranasal immunization with t-gD-IL-2 protected mice from intraperitoneal HSV -1 infections, whereas t-gD-LTB or t-gD alone failed to provide protection against infection. Even in a mouse strain that responded highly to subcutaneously administered gD, intranasally administered t-gD did not elicit antibody responses. The lack of response to gD was clearly abrogated by co-administration with IL-2, and administration of t-gD-IL-2 induced an excellent level of antibody responses in this strain. These results suggest that the IL-2 fusion strategy yields a new type of mucosal immunization, the mechanism of which differs from that speculated for the mucosal adjuvant activity of LTB.

4/AB/21 (Item 1 from file: 35)
DIALOG(R)File 35:Dissertation Abs Online

01642426 AADC646602
GENETICALLY MODIFIED CHOLERA TOXIN B-SUBUNITS: POTENTIAL FOR USE IN VACCINES AND FOR ELUCIDATING TOXIN-RECEPTOR INTERACTIONS (ESCHERICHIA COLI)

Author: BACKSTROM, MALIN
Degree: MED.DR.
Year: 1997
Corporate Source/Institution: GOTEBORGS UNIVERSITET (SWEDEN) (0904)
Source: VOLUME 59/03-C OF DISSERTATION ABSTRACTS INTERNATIONAL. PAGE 571. 72 PAGES
ISBN: 91-628-2398-1
Publisher: DEPT. OF MEDICAL MICROBIOLOGY AND IMMUNOLOGY, GOTEBORG UNIVERSITY, GULDHEDSGATAN 10A, S-413 46 GOTEBORG, SWEDEN

The non-toxic, receptor-binding B-subunit of cholera toxin (CTB) is a good mucosal immunogen, which is included in recently developed peroral vaccines against cholera and enterotoxigenic Escherichia coli (ETEC). In the first part of this study, CTB was investigated as a carrier for foreign peptide epitopes from HIV -1 gp120, hepatitis B virus pre-S(2) or ETEC heat-stable enterotoxin, which were genetically inserted at an internal site within CTB, or fused to the N-terminus. The resulting hybrid proteins retained important functional characteristics of CTB including pentamer formation and binding to GM1 ganglioside receptors, and they reacted with antibodies to the attached foreign epitopes. Mice immunised with the hybrid proteins had high titers of IgG antibody responses against CTB in serum and lower magnitudes of antibody responses against the heterologous peptides.

Second, hybrid proteins between CTB and the closely related B-subunit of Escherichia coli heat-labile enterotoxin (LTB) were constructed by substituting CTB amino acids with those at the corresponding positions in LTB, in order to obtain B-subunits which displayed both cross-reactive and toxin-specific epitopes. Mice immunised with hybrid B-subunits with LTB substitutions in the 1-25 and 94-95 regions, but not those immunised with CTB, had high levels of LTB-specific antibodies in serum, indicating that the hybrid proteins displayed novel LTB-specific epitopes, which were not present in CTB. The sera were also able to neutralise the toxic effects of both CT and LT better than sera from mice immunised with either CTB or LTB. The hybrid B-subunits are promising candidates to be included in an ETEC vaccine or in a combined cholera and ETEC vaccine.

Hybrid CT/LT B-subunits with LTB substitutions in the 1-25, 75-83 or 94-95 regions, or in combinations of these, were also used to investigate the influence of heterologous LTB amino acid substitutions on the broader receptor-specificity of LT compared to CT. The ability of the mutant B-subunits to bind to different preparations of receptors from rabbit intestine, and to isolated glycosphingolipids, was analysed. The results suggested that the interactions of LTB with different classes of non- GM1 receptors are influenced by different amino acids in the protein.

01129214 AAD9029316

STRUCTURAL AND IMMUNOCHEMICAL ANALYSIS OF THE PRE-S DOMAINS OF THE HEPATITIS B SURFACE ANTIGEN

Author: HU, PEISHENG

Degree: PH.D.
Year: 1990
Corporate Source/Institution: VIRGINIA COMMONWEALTH UNIVERSITY (2383)
Source: VOLUME 51/06-B OF DISSERTATION ABSTRACTS INTERNATIONAL.
PAGE 2865. 183 PAGES

Five peptides corresponding to pre-S sequences of hepatitis B surface antigen (HBsAg) have been synthesized. The antibodies against these peptides were produced from rabbits and showed to be able to recognize native HBsAg. A monoclonal antibody 1C10 which is specific to the pre-S2 region has been found and characterized. Competition assays and chemical modification studies have shown that Arg 124 and/or Arg 126 of pre-S2 domain may be critical for the antigenicity of pre-S2. Radioimmunoassays for the determination of the relative amounts of hepatitis B viral pre-S proteins have been developed and used to examine hepatitis B surface antigen positive human plasma samples for the presence and relative amount of pre-S proteins. It was found that there is no correlation between the presence of the pre-S proteins and HBeAg status of the plasma. Limited proteolysis with eight different proteases demonstrated that the pre-S domains of HBsAg are exposed on the surface of the particle structure and that the junction region of the pre-S1 and pre-S2 domains is most sensitive to protease. Studies on the HBsAg reaction with polymerized human serum albumin (pHSA) showed that the pHSA binds to native and recombinant HBsAg particles which contain the preS sequence but does not bind to the trypsin-digested or recombinant HBsAg particles which have no preS sequence. In addition, the pHSA-HBsAg binding can be inhibited by one of the synthetic preS peptides, P 109-133, and its antiserum, suggesting that the binding site is located within the residues between 109 and 133 of preS domain of HBsAg.

A chimeric protein which contains the pre-S2 antigenic determinant and the complete cholera toxin B unit has been constructed and expressed in

E. coli. The purified protein was shown to have the expected amino acid sequence by Edman degradation. Moreover, the protein retains the oligomeric structure of native cholera toxin B subunit and the GM1 ganglioside binding activity. In addition, this molecule is recognized by both antibodies to cholera toxin B and antibodies to preS2, and retains the polymerized albumin binding activity of pre-S2. Preliminary immunization studies have shown that mice fed with purified chimeric protein were able to produce antibodies which recognize native cholera toxin B, the chimeric protein, and the native HBsAg containing pre-S2 domain. These studies demonstrate the feasibility of development of an oral vaccine for hepatitis B.

4/AB/23 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07705836 EMBASE No: 1999187237
Human erythrocyte glycosphingolipids as alternative cofactors for human immunodeficiency virus type 1 (HIV -1) entry: Evidence for CD4-induced interactions between HIV -1 gp120 and reconstituted membrane microdomains of glycosphingolipids (Gb3 and GM3)
Hammache D.; Yahi N.; Maresca M.; Pieroni G.; Fantini J.
J. Fantini, Lab. Biochim. et Biol. de la Nutri., ESA-CNRS 6033, Faculte des Sciences de St Jerome, 13397 Marseille Cedex 20 France
AUTHOR EMAIL: JACQUES.FANTINI@LBBN.u-3mrs.fr
Journal of Virology (J. VIROL.) (United States) 1999, 73/6 (5244-5248)
CODEN: JOVIA ISSN: 0022-538X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 30

Glycosphingolipids from human erythrocytes mediate CD4-dependent fusion with cells expressing human immunodeficiency virus type 1 (HIV -1) envelope glycoproteins. To identify the glycosphingolipid(s) which participates in the fusion process, we have analyzed the interaction of HIV -1 gp120 (X4 and R5X4 isolates) with reconstituted membrane microdomains of human erythrocyte glycosphingolipids. We identified globotriaosylceramide (Gb3) and ganglioside GM3 as the main glycosphingolipids recognized by gp120. In the presence of CD4, Gb3 interacted preferentially with the X4 gp120, whereas GM3 interacted exclusively with the R5X4 gp120. These data suggest that glycosphingolipid microdomains are required in CD4-dependent fusion and that Gb3 and/or GM3 may function as alternative entry cofactors for selected HIV -1 isolates.

4/AB/24 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07649142 EMBASE No: 1999128225
Novel enabling technologies for vaccine development
Lycke N.
N. Lycke, Dept. of Medical Microbiol./Immunol., University of Goteburg, Guldhedsgatan 10, SE 413 46 Goteborg Sweden
AUTHOR EMAIL: Nils.Lycke@microbio.gu.se
IDrugs (IDRUGS) (United Kingdom) 1999, 2/4 (295-298)
CODEN: IDRUF ISSN: 1369-7056
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

This was a very well-organized meeting with a highly attractive program featuring some of the leading people in current vaccine development. A special focus was given to novel adjuvant research and the possibility of developing combination vaccines. Close to 150 participants from academia and industry gathered in the excellent conference center of the Royal Society and the two-day sessions were superbly chaired by Professor Myron Levine, (Center for Vaccine Development (CVD), University of Maryland, Baltimore, USA) and Dr Ronald Ellis, (BioChem Pharma Inc, Boston, MA, USA).

4/AB/25 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

05221533 EMBASE No: 1992361767
E . coli heat-labile enterotoxin B subunit as a carrier for delivery of a peptide with anti- HSV activity
Marcello A.; Palu G.; Hirst T.R.
Biological Laboratory, University of Kent,Canterbury, Kent CT2 7NJ United Kingdom
Biochemical Society Transactions (BIOCHEM. SOC. TRANS.) (United Kingdom) 1992, 20/4 (311S)
CODEN: BCSTB ISSN: 0300-5127
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH

4/AB/26 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

14391929 PASCAL No.: 00-0045905
Formulation of HIV -envelope protein with lipid vesicles expressing ganglioside GM1 associated to cholera toxin B enhances mucosal immune responses
TIANSHUN LIAN; BUI T; HO R J Y
Department of Pharmaceutics, School of Pharmacy, University of Washington, Box 357610, H272 Health Sciences Building, Seattle, WA 98195-7610, United States
Journal: Vaccine, 1999, 18 (7-8) 604-611
Language: English
Taking advantage of the ability of pentameric cholera toxin B subunit (CTB) to bind selectively to GM1 , we developed recently a CTB-mediated GM 1 lipid vesicle delivery system to target drugs and proteins to mucosal tissues (1). In this report, we present the use of such a strategy to deliver an HIV envelope protein (HIV -env) to mucosal tissues via intranasal route. Intranasal administration of a recombinant HIV envelope protein formulated in CTB-associated GM 1 lipid vesicles enhanced mucosal IgA antibody responses detected in the nasal and gut tissues, compared to that of control animals immunized with antigen formulated in GM1 -free vesicles with CTB or formulated in alum-associated vesicles with CTB. We found a nearly 2- to 3-fold enhancement in IgA antibody titers detected both in nasal and gut tissues using the CTB-GMI lipid vesicle delivery system, compared to using the GM1 -free lipid vesicle system. Intranasal administration of HIV -env formulated in the CTB-associated GM1 vesicles also induced a significant level of serum IgG and cellular immune responses against HIV -env. IgG isotype analysis indicates that CTB in GM1 vesicle delivery system enhanced both IgG1 and IgG2a while CTB in alum formulation enhanced only IgG1. However, IgA and IgG antibody responses against CTB were similar for GM1 vesicles regardless of whether HIV -env was present in the vaccine formulation. Collectively, these data indicate that delivery

of HIV -env to mucosal epithelial cells with CTB-associated GM 1 lipid vesicles enhanced mucosal and systemic immune responses against the HIV -envelope protein. It is possible that both the CTB-mediated targeted delivery of antigen-loaded GM 1 lipid vesicles and mucosal adjuvanticity of CTB may be involved in enhancing the immune responses.

4/AB/27 (Item 2 from file: 144)
DIALOG(R)File 144:Pascal

12505985 PASCAL No.: 96-0176271
Gene fusion of cholera toxin B subunit and HBV PreS2 epitope and the antigenicity of fusion protein
CHENG-HUA S; CHENG C; JING-SHENG Z; JIEZHI L; QING-JUN M
Molecular Genetics Center, Institute of Biotechnology, Beijing 100850, China
Journal: Vaccine, 1995, 13 (10) 933-937
Language: English
A unique EcoRI site was introduced at the 3' end of cholera toxin B subunit (CTB) gene by site-directed mutagenesis, polynucleotides encoding 120-145aa epitope of HBV PreS2 were chemically synthesized and fused to the 3' end of cholera toxin B subunit gene. The fused gene was over-expressed (about 30 mu g ml SUP - SUP 1) in E. coli, and more than 95% of the fusion protein was secreted into the medium. The fusion protein expressed was purified by affinity chromatography. The chimera protein obtained bound to ganglioside GM1 , and had the antigenicity of both cholera toxin B subunit and HBV PreS2 as confirmed by ELISA. After mice were immunized intramuscularly with the fusion protein, anti-CTB antibody and anti-PreS2 antibody were produced. These results indicated that the fusion protein retained not only the biological function of CTB but also the antigenicity and the immunogenicity of cholera toxin B subunit and HBV PreS2 epitope. This work provided a sound basis for further studies on the construction of engineered peptide vaccine.

4/AB/28 (Item 1 from file: 351)
DIALOG(R)File 351:Derwent WPI

014065919
WPI Acc No: 2001-550132/200161
XRAM Acc No: C01-163771
Spray-dried lipid microparticle composition useful for introducing therapeutic or biologically active agents into a cell, e.g., the introduction of an agent to suppress pathogenic T cells
Patent Assignee: ALLIANCE PHARM CORP (ALLI-N)
Inventor: BOT A; DELLAMARY L; SMITH D; WOODS C M
Number of Countries: 094 Number of Patents: 002
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200164254	A2	20010907	WO 2001US6532	A	20010227	200161	B
AU 200141882	A	20010912	AU 200141882	A	20010227	200204	

Priority Applications (No Type Date): US 2000515359 A 20000229
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200164254	A2	E	46	A61K-047/00	

Designated States (National): AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA

CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
AU 200141882 A A61K-047/00 Based on patent WO 200164254

Abstract (Basic): WO 200164254 A2
Abstract (Basic):

NOVELTY - A Spray-Dried Lipid Microparticle (SDLM) composition (I), comprising one or more phospholipids, a therapeutic or biologically active agent, and at least one ligand that binds to a cell surface receptor is new

ACTIVITY - Cytostatic; antirheumatic; antiarthritic; antidiabetic; neuroprotective; immunomodulatory.

No supporting data given.

MECHANISM OF ACTION - Class I or Class II major histocompatibility complex (MHC) immune response inducer; activity of T suppressor cells enhancer; activity of pathogenic T cells suppressor; production of suppressor cytokines by antigen presenting cells, inducer; gene therapy.

Airway antigen presenting cell (APC) were isolated from BALB/c mice by standard bronchoalveolar lavage using normal phosphate buffered saline (PBS). The recovered cells were washed with 4degreesC-cold cell culture medium (HL-1) twice and incubated in 96-well flat-bottom plates (1x105 cells/well) with various amounts of dried-SDLM, corresponding to defined quantities of viral antigen. After 1 hour incubation at 37degreesC under mild horizontal shaking conditions (30 rpm), the non-adherent cells and lipid debris were washed off by repeated, gentle addition and removal of HL-1 medium. T cell hybridoma (16-2-6) specific for HA 110-120 epitope of WSN virus were added to the plastic-adherent cells (x104 TcH/well in 100 microl of HL-1 medium). After 12-hour incubation at 37degreesC and 5% CO2, the cells were fixed with glutaraldehyde/formaldehyde and X-gal substrate was added. The results showed that addition of a ligand to SDLM improved the efficiency of antigen presentation by bronchoalveolar phagocytes, as compared to non-ligand engineered SDLM with antigen.

USE - (I) is useful for introducing a therapeutic or biologically active agent into a cell of a subject, where the ligand (an immunoglobulin such as IgG, IgM, IgA, IgE or IgD) and the agent are coupled such that upon binding of the ligand to the cell surface receptor, a ligand-agent-receptor complex is formed and subsequently internalized by the cell, thereby resulting in introduction of the agent into the cell e.g., a macrophage or any antigen presenting cell (APC). The method is preferably useful for introducing an antigen which upon internalization induces a Class I major histocompatibility complex (MHC) (CD8+ cytotoxic T lymphocyte (CTL)) response or Class II MHC response immune response in the subject. The introduction of the agent alternately results in suppression of pathogenic T cells (all claimed).

(I) is also useful for selectively inhibiting or killing the growth of neoplastic cells. The methods to suppress activity of pathogenic T cells can be employed to treat autoimmune diseases e.g., Type I diabetes, multiple sclerosis, rheumatoid arthritis, etc. (I) is also employed for DNA immunization methods, and for introducing therapeutic genes for gene therapy techniques.

ADVANTAGE - (I) is biocompatible and is targetable to a internalizable cell surface receptor. Use of (I) allows improved and effective immune response to be induced against the infectious agents.

pp; 46 DwgNo 0/12

4/AB/29 (Item 2 from file: 351)
DIALOG(R)File 351:Derwent WPI

013167654
WPI Acc No: 2000-339527/200029
XRAM Acc No: C00-102997
Vaccine adjuvant containing a toxin whose toxicity is attenuated by removal of lysine, serine or glutamic acid residues for nasal or percutaneous vaccination with an effective degree of immune enhancement
Patent Assignee: KITASATO INST (KITA)
Inventor: AIZAWA C; HATTORI N; OMURA S; SATO T; SUZUKI Y; TANAKA Y; WATANABE K
Number of Countries: 029 Number of Patents: 006
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 200023107	A1	20000427	WO 99JP5789	A	19991020	200029	B
AU 9962274	A	20000508	AU 9962274	A	19991020	200037	
EP 1123711	A1	20010816	EP 99949324	A	19991020	200147	
			WO 99JP5789	A	19991020		
BR 9915533	A	20011106	BR 9915533	A	19991020	200175	
			WO 99JP5789	A	19991020		
JP 2000576880	X	20020122	WO 99JP5789	A	19991020	200211	
			JP 2000576880	A	19991020		
KR 2001083916	A	20010903	KR 2001704935	A	20010420	200217	

Priority Applications (No Type Date): JP 98300219 A 19981021
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 200023107	A1	J	55	A61K-039/39	
Designated States (National): AU BR CA CN IN JP KR MX RU US					
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
AU 9962274	A			A61K-039/39	Based on patent WO 200023107
EP 1123711	A1	E		A61K-039/39	Based on patent WO 200023107
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
BR 9915533	A			A61K-039/39	Based on patent WO 200023107
JP 2000576880	X			A61P-033/02	Based on patent WO 200023107
KR 2001083916	A			A61K-039/39	

Abstract (Basic): WO 200023107 A1
Abstract (Basic):
NOVELTY - A vaccine adjuvant comprising an attenuated toxin having toxicity reduced to less than 1/2000 of its natural toxicity by removal of lysine, glutamic acid and/or serine residues from its natural sequence or its subunits, is new.
DETAILED DESCRIPTION - AN INDEPENDENT CLAIM is also included for cover vaccines containing the adjuvant together with an immune antigen.

USE - The new adjuvant is useful for the production of vaccines for nasal, oral or percutaneous administration having a low toxicity but high immune enhancement.
pp; 55 DwgNo 0/5

4/AB/30 (Item 3 from file: 351)
DIALOG(R)File 351:Derwent WPI

013051662
WPI Acc No: 2000-223517/200019
XRAM Acc No: C00-068140
Vaccines comprise toxins and an agent with Gb3 or GM1 -binding activity or an agent which effects the intracellular signaling mediated by Gb3 or GM1 -binding
Patent Assignee: UNIV BRISTOL (UYBR-N)
Inventor: BIRD L A; HIRST T R; MORGAN A; WILLIAMS N A; WILSON A D; HIRST R T; WILLIAM N A
Number of Countries: 087 Number of Patents: 010
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9958145	A2	19991118	WO 99GB1461	A	19990510	200019	B
AU 9939394	A	19991129	AU 9939394	A	19990510	200019	
BR 9910305	A	20010109	BR 9910305	A	19990510	200106	
			WO 99GB1461	A	19990510		
NO 200005599	A	20010108	WO 99GB1461	A	19990510	200109	
			NO 20005599	A	20001106		
EP 1075274	A2	20010214	EP 99922284	A	19990510	200111	
			WO 99GB1461	A	19990510		
GB 2353472	A	20010228	WO 99GB1461	A	19990510	200113	
			GB 200027072	A	20001106		
CZ 200004147	A3	20010516	WO 99GB1461	A	19990510	200132	
			CZ 20004147	A	19990510		
KR 2001043441	A	20010525	KR 2000712486	A	20001108	200168	
CN 1308546	A	20010815	CN 99808403	A	19990510	200174	
ZA 200006160	A	20011224	ZA 20006160	A	20001031	200212	

Priority Applications (No Type Date): GB 9812316 A 19980608; GB 989958 A 19980508; GB 9811954 A 19980603
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9958145	A2	E	63	A61K-039/00	
Designated States (National): AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW					
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
AU 9939394	A				Based on patent WO 9958145
BR 9910305	A			A61K-039/00	Based on patent WO 9958145
NO 200005599	A			A61K-000/00	
EP 1075274	A2	E		A61K-039/12	Based on patent WO 9958145
Designated States (Regional): AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
GB 2353472	A			A61K-039/12	Based on patent WO 9958145
CZ 200004147	A3			A61K-039/12	Based on patent WO 9958145
KR 2001043441	A			A61K-039/00	
CN 1308546	A			A61K-039/12	
ZA 200006160	A		77	A61K-000/00	

Abstract (Basic): WO 9958145 A2
Abstract (Basic):

NOVELTY - The use of a composition (I) comprising Escherichia coli heat-labile enterotoxin B (EtxB), cholera toxin B (CtxB) or E . coli verotoxin B (VtxB) free from whole toxin, another agent with GM1 -binding activity, or another agent with Gb3 -binding activity, or an agent affecting intracellular signals mediated by GMi or Gb3 binding, as an immunomodulator for an infectious disease vaccine, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the

following:

(1) a vaccine composition for use against an infectious disease, which infectious disease is caused by an infectious agent, wherein the vaccine composition comprises an antigenic determinant and an immunomodulator of the novelty;

(2) a kit for vaccination of a mammalian subject against an infectious disease, comprising (I), and an antigenic determinant of the infectious disease, for co-administration with the vaccine immunomodulator;

(3) a method of preventing or treating a disease in a host, comprising inoculating the host with a vaccine comprising at least one antigenic determinant and an immunomodulator of the novelty; and

(4) a vaccine composition for use against an infectious disease caused by an infectious agent, comprising (I), where the antigenic determinant is of an infectious agent and the immunomodulator prolongs presentation of the antigenic determinant and gives sustained immunological memory.

ACTIVITY - Antiinfectious; virucide; antibacterial; protozoacide.

MECHANISM OF ACTION - Vaccine.

USE - The vaccine is used to treat infectious diseases. The infectious disease is caused by an infectious agent selected from herpes simplex virus (HSV)-1, HSV -2, Epstein Barr virus (EBV), zoster virus (VZV), cytomegalo virus (CMV), HHV-6, HHV-7 and HHV-8, or an influenza virus, especially parainfluenza virus, a respiratory syncytial virus, a hepatitis virus, e.g. A, B, C and D viruses, meningitis , Neisseria meningitides , Haemophilus influenzae type B and Streptococcus pneumoniae . The infectious disease is pneumonia or a respiratory tract infection. The infectious disease is caused by an infectious agent selected from Streptococcus pneumoniae , Legionella pneumophila and Mycobacterium tuberculosis . The infectious disease is a sexually-transmitted disease, e.g. Neisseria gonnorheae , human immunodeficiency virus (HIV)-1, HIV -2 and Chlamydia trachomatis. The infectious disease is a gastrointestinal disease caused by enteropathogenic, enterotoxigenic, enteroinvasive, enterahaemorrhagic and enteroaggregative E. coli, rotavirus, Salmonella enteritidis, Salmonella typhi, Helicobacter pylori, Bacillus cereus, Campylobacter jejuni and Vibrio cholerae. The infectious disease is a superficial infection caused by an infectious agent selected from Staphylococcus aureus, Streptococcus pyogenes and Streptococcus mutans. The infectious disease is a parasitic disease caused by selected from malaria, Trypanasoma spp., Toxoplasma gondii, Leishmania donovani and Oncocerca spp. (all claimed).

pp; 63 DwgNo 0/15

4/AB/31 (Item 4 from file: 351)
DIALOG(R)File 351:Derwent WPI

012624225
WPI Acc No: 1999-430329/199936
XRAM Acc No: C99-126824
Use of agents modulating ganglioside associated activity for treating allergic or hypersensitivity conditions
Patent Assignee: ORATOL LTD (ORAT-N); UNIV BRISTOL (UYBR-N)
Inventor: BIENENSTOCK J; HIRST T R; WILLIAMS N A
Number of Countries: 085 Number of Patents: 005
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9934817	A1	19990715	WO 99GB70	A	19990108	199936	B
AU 9919782	A	19990726	AU 9919782	A	19990108	199952	

GB 2347625	A	20000913	WO 99GB70	A	19990108	200046
			GB 200014295	A	20000612	
EP 1044014	A1	20001018	EP 99900567	A	19990108	200053
			WO 99GB70	A	19990108	
JP 2002500194	W	20020108	WO 99GB70	A	19990108	200206
			JP 2000527265	A	19990108	

Priority Applications (No Type Date): GB 98487 A 19980109
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9934817	A1	E	45	A61K-038/16	
AU 9919782	A			A61K-038/16	Based on patent WO 9934817
GB 2347625	A			A61K-038/16	Based on patent WO 9934817
EP 1044014	A1	E		A61K-038/16	Based on patent WO 9934817
JP 2002500194	W		47	A61K-045/00	Based on patent WO 9934817

Designated States (National): AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
Designated States (Regional): AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE

Abstract (Basic): WO 9934817 A1
Abstract (Basic):

NOVELTY - The use of an agent (A) in the manufacture of a medicament to affect an allergic condition and/or a hypersensitivity condition, is new.

DETAILED DESCRIPTION - The agent is capable of modulating a ganglioside associated activity and is not coupled to an antigen. The modulation of the ganglioside, such as GM1 , associated activity affects an allergic condition and/or hypersensitivity condition.

An INDEPENDENT CLAIM is also included for the following:

(1) an assay method for identifying an agent as in (A) that is capable of affecting an allergic condition and/or a hypersensitivity condition, where the assay method comprises:

(a) contacting an agent with a ganglioside receptor;

(b) determining whether the agent modulates a ganglioside associated activity, such that the modulation of the ganglioside associated activity is indicative that the agent may be capable of affecting an allergic condition and/or a hypersensitivity condition; and where the agent is not coupled to an antigen;

(2) a process comprising:

(a) performing the assay of (1);

(b) identifying one or more agents capable of modulating a ganglioside associated activity;

(c) optionally identifying one or more agents that modulates a ganglioside associated activity;

(d) preparing a composition comprising one or more identified agents;

(3) an agent identified by the process of (2); and

(4) a method of affecting an allergic condition or a hypersensitivity condition with one or more agents, where the agent is capable of modulating a ganglioside associated activity in an in vitro assay method such as that of (1).

ACTIVITY - Antiallergic; Antiasthmatic; Antiinflammatory; Dermatological.

MECHANISM OF ACTION - None given.

USE - The agents can be used for treating allergic and/or hypersensitivity conditions, e.g. asthma, allergic cough, allergic

rhinitis and conjunctivitis, atopic eczema and dermatitis, uticaria, hives , insect bite allergy, dietary allergy (peanut, fish, milk, wheat etc), drug allergies or contact hypersensitivity induced by plant poison ivy.
pp; 45 DwgNo 0/0

4/AB/32 (Item 5 from file: 351)
DIALOG(R)File 351:Derwent WPI

012457923
WPI Acc No: 1999-264031/199922
XRAM Acc No: C99-077933
XRPX Acc No: N99-196671
Method of expressing cholera toxin B subunit protein in transgenic plants useful for producing oral vaccines
Patent Assignee: UNIV LOMA LINDA (UYLO-N)
Inventor: ARAKAWA T; CHONG D; LANGRIDGE W H R; MERRITT J L
Number of Countries: 029 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9918225	A1	19990415	WO 98US21237	A	19981007	199922	B
AU 9910724	A	19990427	AU 9910724	A	19981007	199936	
ZA 9809685	A	20000531	ZA 989685	A	19981023	200032	N

Priority Applications (No Type Date): US 9761265 P 19971007; ZA 989685 A 19981023
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9918225	A1	E	54	C12N-015/82	
Designated States (National): AU BR CA CN CZ HU JP KR NZ SK					
Designated States (Regional): AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
AU 9910724	A				Based on patent WO 9918225
ZA 9809685	A		84	A01N-000/00	

Abstract (Basic): WO 9918225 A1
Abstract (Basic):
NOVELTY - A new DNA construct (A) encodes a fusion protein (I) that comprises a subunit (Ia) of an enterotoxin and a signal peptide (Ib).
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) an expression vector containing (A) and an origin of replication functional in Escherichia coli;
(2) strains of E. coli and Agrobacterium tumefaciens transformed with the vector from (1);
(3) a transgenic plant cell, seed and complete plant transformed with (A); and
(4) a method of transforming a host cell with (A) by contacting a plant cell with a strain of A. tumefaciens from (2).
ACTIVITY - Antidiarrheic; antibacterial.
Transformed potato expressing a fusion protein of cholera toxin subunit B (CTB) and the signal peptide Ser-Glu-Lys-Asp-Glu-Leu was fed to mice orally 4 times at weekly intervals, then as a final booster. The animals were fasted for 48 hours, then challenged with 125 ng cholera toxin , delivered to isolated ileal loops. After 24 hours, the amount of fluid accumulated in the loops (a measure of diarrhea) was measured.
Protection against diarrhea was 55% in mice given 30 microgram bacterial CTB, 42% in those given 1 g transgenic potato and 62% in

those given 3 g. The mice fed transgenic potato also showed significant levels of CTB-specific antibodies in their serum and feces.

MECHANISM OF ACTION - Binds specifically to GM1 - ganglioside .

USE - Transgenic plants containing (A) can be used to produce (I) for use as an immunogen. When such plants are fed to mammals or birds, they induce immunity against the enterotoxin, specifically that of cholera. Alternatively, the plants are consumed to provide an adjuvant effect, in conjunction with administration of a live, dead or attenuated dose of pathogen (or its antigenic fragments).

Multimeric CTB can also be used as a carrier peptide for other antigen epitopes providing a low-cost, convenient and effective method for preventing infectious and autoimmmune diseases in man especially in regions of the developing world.

ADVANTAGE - The transgenic plants containing (A) provide edible vaccines for use in regions where the enterotoxin-producing pathogen is endemic. (Ia) produced in plants has the same properties as the native bacterial protein and can be expressed at up to 0.3% total soluble protein. Oral administration generates both serum and intestinal (Ia)-specific antibodies, and although the mucosal response declines gradually, it can be restored with an oral booster. Oral vaccines are also more effective than parenteral vaccination as well as being easier and safer to administer.

pp; 54 DwgNo 0/0

4/AB/33 (Item 6 from file: 351)
DIALOG(R)File 351:Derwent WPI

012360528
WPI Acc No: 1999-166635/199914
Related WPI Acc No: 1992-315939; 1994-359522; 1995-394157; 1996-030801; 1996-049021; 1997-042808; 1998-217031; 1998-311399; 1998-505588; 1999-105118; 1999-579913
XRAM Acc No: C99-048562
XRPX Acc No: N99-121413

Immunosorbent assay for pneumococcal surface protein A antigen or antibody - for diagnosis of infection by Streptococcus pneumoniae

Patent Assignee: UAB RES FOUND (UABR-N)
Inventor: BRILES D E; YOTHER J L
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week
US 5871943	A	19990216	US 91656773	A	19910215	199914 B
			US 92835698	A	19920212	
			US 9372068	A	19930603	
			US 95468718	A	19950606	

Priority Applications (No Type Date): US 92835698 A 19920212; US 91656773 A 19910215; US 9372068 A 19930603; US 95468718 A 19950606
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 5871943	A		22	G01N-033/569	CIP of application US 91656773 Div ex application US 92835698 Cont of application US 9372068

Abstract (Basic): US 5871943 A

NOVELTY - Solid phase immunosorbent assay for detecting a PspA (pneumococcal surface protein A) antibody and antigen is improved by using a truncated form (I) of PspA to coat the solid phase.

DETAILED DESCRIPTION - (I) contains truncated PspA (Ia) containing

the immunoprotective epitopes of the complete protein (up to 90% of PspA but excluding the cell-membrane anchor region) fused to the B subunit of cholera toxin (CTB) which is bound to monosialoganglioside (GM1) coated on the substrate.

The specification includes the sequence, 648 amino acids (aa) of the complete PspA.

USE - The assay is used to diagnose infection by Streptococcus pneumoniae .

ACTIVITY - None given.

MECHANISM OF ACTION - Specific binding interaction.

ADVANTAGE - The use of a fusion between truncated PspA and cholera toxin B subunit (CTB) allows the support to be coated without having to isolate PspA fragments, since CTB binds specifically to ganglioside GM1 coating the solid support.

Dwg.0/7

4/AB/34 (Item 7 from file: 351)
DIALOG(R)File 351:Derwent WPI

011894489
WPI Acc No: 1998-311399/199827
Related WPI Acc No: 1992-315939; 1994-359522; 1995-394157; 1996-030801; 1996-049021; 1997-042808; 1998-217031; 1998-505588; 1999-105118; 1999-166635; 1999-579913
XRAM Acc No: C98-095969
Truncated pneumococcal surface protein and cholera toxin B sub-unit fusion protein - useful as an immunogen against Streptococcus pneumoniae

Patent Assignee: UAB RES FOUND (UABR-N)
Inventor: BRILES D E; YOTHER J L
Number of Countries: 001 Number of Patents: 001
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
US 5753463	A	19980519	US 91656773	A	19910215	199827	B
			US 92835698	A	19920212		
			US 9372065	A	19930603		
			US 95469434	A	19950606		

Priority Applications (No Type Date): US 92835698 A 19920212; US 91656773 A 19910215; US 9372065 A 19930603; US 95469434 A 19950606
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
US 5753463	A		22	C12P-021/02	CIP of application US 91656773 Div ex application US 92835698 Cont of application US 9372065

Abstract (Basic): US 5753463 A

A recombinant DNA molecule encoding a fusion protein comprising a truncated form of pneumococcal surface protein (PspA) and cholera toxin B subunit (CTB) is new, where the DNA molecule comprises a nucleotide sequence encoding the truncated PspA linked by an in-frame genetic fusion to a ctxB gene, and where the truncated PspA contains immunoprotective epitopes and up to 90% of the whole PspA protein, except for the cell membrane anchor region, the whole PspA protein having a defined sequence of 648 amino acids as given in the specification.

Also claimed are:

(a) a mutated strain of Streptococcus pneumoniae containing the recombinant DNA molecule;

(b) plasmid pJY4163; and
(c) a method for producing the fusion protein, comprising transforming a bacterium selected from (a strain of) Streptococcus pneumoniae or (a strain of) E. coli with the recombinant DNA molecule and growing the transformed bacterium to express the fusion protein.
USE - The fusion protein is useful for providing an immunogen to protect neonates and children against S. pneumoniae . Most antigenic proteins of this strain are not immunogenic enough to provide protection. The antigenic epitopes of the fusion protein are directed against capsular polysaccharide antigens of S. pneumoniae , specifically it contains the protective epitopes of PspA. The protein can also be used in solid-phase immunoadsorbent assays, since it is readily bound to supports coated with monosialoganglioside GM1 .
ADVANTAGE - The fusion protein is more immunogenic against S. pneumoniae than using PspA alone as the immunogen.
Dwg.0/7

4/AB/35 (Item 8 from file: 351)
DIALOG(R)File 351:Derwent WPI

010845097
WPI Acc No: 1996-342050/199634
Related WPI Acc No: 1999-418296
XRAM Acc No: C96-108609
New cpd. for treating auto-immune disease - contains collagen coupled to mucosa-binding component, esp. for rheumatoid arthritis
Patent Assignee: ACAD FINLAND (FIFI-N); FIBROGEN INC (FIBR-N)
Inventor: KIVIRIKKO K I; MARTIN G R; NEFF T B; PIEZ K A; PIHLAJANIEMI T Z; PIHLAJANIEMI T A
Number of Countries: 070 Number of Patents: 009
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
WO 9621458	A1	19960718	WO 96US533	A	19960111	199634	B
AU 9646570	A	19960731	AU 9646570	A	19960111	199645	
NO 9703193	A	19970909	WO 96US533	A	19960111	199747	
			NO 973193	A	19970709		
FI 9702929	A	19970910	WO 96US533	A	19960111	199749	
			FI 972929	A	19970710		
EP 805686	A1	19971112	EP 96902148	A	19960111	199750	
			WO 96US533	A	19960111		
BR 9606753	A	19980106	BR 966753	A	19960111	199810	
			WO 96US533	A	19960111		
HU 9800829	A2	19980728	WO 96US533	A	19960111	199842	
			HU 98829	A	19960111		
JP 10512554	W	19981202	JP 96521858	A	19960111	199907	
			WO 96US533	A	19960111		
MX 9705198	A1	19971201	MX 975198	A	19970710	199936	

Priority Applications (No Type Date): US 95370388 A 19950110
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
WO 9621458	A1	E	29	A61K-038/17	

Designated States (National): AL AM AU AZ BB BG BR BY CA CN CZ EE FI GE HU IS JP KG KP KR KZ LK LR LS LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA UZ VN
Designated States (Regional): AT BE CH DE DK EA ES FR GB GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG

AU 9646570	A		Based on patent WO 9621458
EP 805686	A1	E	Based on patent WO 9621458

Designated States (Regional): AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

BR 9606753	A			Based on patent WO 9621458
HU 9800829	A2			Based on patent WO 9621458
JP 10512554	W	31	A61K-038/17	Based on patent WO 9621458
NO 9703193	A		A61K-038/39	
FI 9702929	A		A61K-000/00	
MX 9705198	A1		A61K-038/17	

Abstract (Basic): WO 9621458 A

Cpd. (A) for treating autoimmune disease comprises a collagen molecule (I) linked to a mucosa-binding component (II).

(I) is type II, IX and XI collagen, esp. a variably glycosylated type II deriv. (II) is derived from bacterial toxins or fimbriae, viral attachment proteins or plant lectins and esp. can bind ganglioside GM1 . The binding fragment is most pref. beta subunit of cholera toxin and heat-labile enterotoxin of E. coli. (I) and (II) are chemically linked through standard cross-linking agents, e.g. N-succinimidyl (3-(2-pyridyldithio)propionate) or they are expressed as a single fusion protein by recombinant DNA methods.

USE - (A) is used to treat rheumatoid arthritis and a wide range of other immune system diseases such as bursitis, Crohn's disease, hepatitis , lupus, nephritis, osteoarthritis, psoriasis etc. The specification includes a table indicating which types of collagen are suitable for particular conditions. Admin. of (A) induces immunological tolerance against the tissue from which (I) is derived. (A) are generally administered orally so that it contacts intestinal lymphoid tissue, pref. at 0.001-200 mg (I) per day. Topical, inranasal, parenteral and inhalation admin. are also contemplated.

Dwg.0/0

4/AB/36 (Item 9 from file: 351)
DIALOG(R)File 351:Derwent WPI

010037654
WPI Acc No: 1994-305365/199438
XRAM Acc No: C94-139086

Fused protein based on endotoxin B sub-unit - and active aminoacid fragment, with glycine-proline hinge, used to treat virus diseases including HIV , polio, rhinovirus etc.

Patent Assignee: WELLCOME FOUND LTD (WELL); GLAXO WELLCOME INC (GLAX)
Inventor: CHARLES I G; FAIRWEATHER N F; LIPSCOMBE M J
Number of Countries: 002 Number of Patents: 003
Patent Family:

Patent No	Kind	Date	Applicat No	Kind	Date	Week	
JP 6206900	A	19940726	JP 92192643	A	19920610	199438	B
US 5589384	A	19961231	US 92896003	A	19920611	199707	
			US 94237716	A	19940502		
JP 3267333	B2	20020318	JP 92192643	A	19920610	200222	

Priority Applications (No Type Date): GB 9112553 A 19910611
Patent Details:

Patent No	Kind	Lan	Pg	Main IPC	Filing Notes
JP 6206900	A		16	C07K-015/12	
US 5589384	A		15	C12N-015/61	Cont of application US 92896003
JP 3267333	B2		16	C07K-019/00	Previous Publ. patent JP 6206900

Abstract (Basic): JP 6206900 A

Fused protein comprises a biologically active amino acid sequence

bound to the C-terminal of the amino acid sequence in B subunit of enterotoxin is new. The enterotoxin terminal forms a ADP-ribosyl bond with GTPase. The biologically active amino acid sequence is bound with the sufficient C-terminals of amino acid sequence in the B subunit via intervening hinge composed of 2-8 glycine-proline repetitive sequence.

Pref. active aminoacid sequence is an epitope obtd. from an agent causing respiratory or digestive disease, esp. HIV , hepatitis A or B virus, rhinovirus, herpes simplex, polio, foot and mouth disease, influenza, coxsackie, chlamydia or whooping cough virus; and endotoxin is from cholera vibrio or E. coli.

USE/ADVANTAGE - Prevention and treatment of diseases caused by the viruses given above. (Reissue of the entry advised in week 9434 based on complete specification).

Dwg.0/6

Abstract (Equivalent): US 5589384 A

A fusion protein comprising the following elements linked in an N-terminal to C-terminal direction:

(A) sufficient of the B subunit of cholera toxin or heat-labile enterotoxin of Escherichia coli such that the fusion protein forms a pentamer complex and binds to GM1 - ganglioside ;

(B) a hinge of from two to eight directly linked glycineproline repeats; and

(C) a predetermined antigen or epitope of a human or animal pathogen, which antigen or epitope effects an immune response.

Dwg.0/6

4/AB/37 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res

0226477 DBA Accession No.: 98-08074 PATENT
Truncated pneumococcal surface protein and cholera toxin B subunit fusion protein - vector plasmid pYJ4163-mediated prpA gene expression in Escherichia coli or Streptococcus pneumoniae , used in infection recombinant vaccine

AUTHOR: Briles D E; Yother J L
CORPORATE SOURCE: Birmingham, AL, USA.
PATENT ASSIGNEE: UAB-Res.Found. 1998

PATENT NUMBER: US 5753463 PATENT DATE: 980519 WPI ACCESSION NO.: 98-311399 (9827)
PRIORITY APPLIC. NO.: US 469434 APPLIC. DATE: 950606
NATIONAL APPLIC. NO.: US 469434 APPLIC. DATE: 950606
LANGUAGE: English

ABSTRACT: A new recombinant DNA molecule encodes a fusion protein consisting of a truncated form of pneumococcal surface protein (PspA) and cholera toxin -B subunit (CTB). The new DNA consists of a DNA sequence encoding truncated PspA linked by an in-frame genetic fusion to a ctxB gene, where the truncated PspA contains immunoprotective epitopes and up to 90% of the whole PspA protein, except for the cell membrane anchor region. The PspA protein has a defined 648 amino acid protein sequence. Also claimed are: a Streptococcus pneumoniae mutant containing the recombinant DNA; plasmid pJY4163; and a method for producing the fusion protein which involves transforming S. pneumoniae or Escherichia coli with the recombinant DNA molecule and growing the transformed bacterium to obtain the fusion protein. The fusion protein may be used to provide an immunogen to protect neonates and children against S. pneumoniae infection. The protein may also be used in solid-phase immunoadsorbent assays as it is readily bound to supports coated with monosialoganglioside GM1 . (22pp)

4/AB/38 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res

0165994 DBA Accession No.: 94-08545
Development of recombinant viral vaccines based on Escherichia coli heat-labile enterotoxin as a mucosal adjuvant - hemagglutinin subunit-1 and thermostable enterotoxin-A chain fusion protein production by vector expression in Escherichia coli for use as a HIV virus-1 recombinant vaccine
AUTHOR: de Haan L; Verweij W R; Holtrop M; Lubberts E; Agsteribbe E; Daemen T
CORPORATE AFFILIATE: Univ.Groningen Univ.Washington-Seattle
CORPORATE SOURCE: Department of Physiological Chemistry, Groningen Institute for Drug Studies (GIDS), University of Groningen, Bloemsingel 10, 9712 KZ Groningen, The Netherlands.
JOURNAL: Pharm.World Sci. (16, 3, Suppl.C, C9) 1994
CODEN: PWSCED
LANGUAGE: English
ABSTRACT: Recombinant viral vaccines, based on the use of non-toxic variants of heat-labile enterotoxin with genetically coupled viral antigenic determinants, to induce a high systemic IgG response and a strong mucosal secretory IgA response, against the inserted viral epitopes, were constructed. Molecular modelling studies were used to select appropriate sequences of the hemagglutinin subunit-1 and suitable insertion sites in the A chain of the heat-labile enterotoxin. A hybrid molecule was constructed in which the major part of the A chain of the heat-labile enterotoxin was replaced by the selected hemagglutinin subunit-1 fragment. The construct was expressed in Escherichia coli, and the fusion protein maintained GM1 -binding activity, indicating an intact B5-pentamer structure. Purification of the fusion protein is currently in progress. On the basis of the 3 dimensional structure of heat-labile enterotoxin, an exposed loop on the B subunit was selected for insertion of the HIV virus-1 gp120 V3 loop, which would not affect its GM1 -binding capacity. Cloning and expression of this gene construct are in progress. (0 ref)

4/AB/39 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res

0131890 DBA Accession No.: 92-04382
Gene fusion of cholera toxin B subunit with HBV PreS epitope and overexpression in E. coli - toxin B subunit expression as hepatitis B virus preS epitope fusion protein in Escherichia for bivalent recombinant vaccine application (conference abstract)
AUTHOR: Chengua S; Chen C; Jingshen Z; Quingjun M
CORPORATE SOURCE: Biotechnology Institute, Academy of Military Medical Sciences, PO Box 130(8), Beijing, People's Republic of China.
JOURNAL: Vaccine (10, 4, 282) 1992
CODEN: VACCDE
LANGUAGE: English
ABSTRACT: Cholera toxin B subunit (CT-B) is a potent and safe adjuvant which augments the production of antibodies in serum and IgA antibodies in mucosal secretion. A unique EcoRI restriction site was constructed near to the C-terminal of the CT-B gene by site-directed mutagenesis, and a plasmid vector was constructed for a gene fusion that overexpressed the CT-B and certain antigenic determinants. 2 Antigenic determinant gene fragments of hepatitis B virus (HBV) preS (12-47,

120-145) were synthesized and cloned into the vector. The fused gene was overexpressed in E. coli and the fusion protein was secreted into the medium. The fusion protein bound to GM1 and reacted with both anti-CTB monoclonal antibodies and also with anti-PreS monoclonal antibodies. It provides an approach to the construction of a bivalent vaccine against both cholera and HBV infections. (0 ref)

4/AB/40 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res

0109640 DBA Accession No.: 90-12331
Construction of an Escherichia coli LT-B vector for expression of foreign antigenic determinant genes - heat-labile enterotoxin gene fusion construction in vector plasmid pYA2906 and expression in Salmonella typhimurium vaccine strain (conference abstract)
AUTHOR: Jagusztyn-Krynicka E K; Clark-Curtiss J E
CORPORATE SOURCE: Washington University, St. Louis, MO, USA.
JOURNAL: Abstr.Annu.Meet.Am.Soc.Microbiol. (90 Meet., 120) 1990
CODEN: 0005M
LANGUAGE: English
ABSTRACT: A new expression cloning vector, plasmid pYA2906, was constructed which allowed translational fusion of genes encoding foreign epitopes and the gene encoding the B subunit of the Escherichia coli heat-labile enterotoxin (LT-B). A 584 Sau3A-MaeI DNA fragment from plasmid pEWD299 was cloned into BamHI- and PstI-cut plasmid pYA810 using a 38 bp linker. The presence of the linker at the 3' end of the LT-B gene provides unique MluI and ApaLI restriction sites and 3 translation stop codons, each in a different reading frame. The LT-B gene on pYA2906 is expressed at a high level in avirulent Salmonella typhimurium delta-crp delta-cya delta-asd oral vaccine strain chi4072. Alterations in the C-terminus domain of LT-B did not affect important properties of the protein. The 11.5 kDa protein produced by cells with pYA2906 is secreted into the periplasm where it pentamerizes. Fusion of the LT-B gene with Streptococcus mutans and Mycobacterium leprae genes is being used to test the immunogenic properties and the affinities of the proteins specified by the vector to GM1 ganglioside and agarose. (0 ref)

4/AB/41 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res

0080370 DBA Accession No.: 88-11219
Construction of a chimeric plasmid expressing glycoprotein B (gB) of herpes simplex virus type 1 and heat-labile enterotoxin (LT-B) of Escherichia coli - expression in Escherichia coli and Salmonella enteriditis (conference abstract)
AUTHOR: Childress A M; Clements J D
CORPORATE SOURCE: Tulane Univ.Schl. of Med., New Orleans, LA, USA.
JOURNAL: Abstr.Annu.Meet.Am.Soc.Microbiol. (88 Meet., 316) 1988
CODEN: 0005M
LANGUAGE: English
ABSTRACT: Glcoprotein gB1, one of the major envelope proteins, coded for by herpes simplex virus type 1 (HSV -1), is important for virus entry into the cell and stimulation of the host immune response. Plasmid pAC61 was constructed encoding production of a possible fusion polypeptide consisting of the binding subunit of the heat-labile enterotoxin (LT-B) of Escherichia coli and HSV -1 gB. The gene

encoding gB1 was isolated, flanked with BamHI linkers, and ligated into the BamHI site of plasmid pFS2.2. Plasmid pFS2.2 was a plasmid pUC19 derivative containing the LT-B gene with the termination codon removed and a polylinker inserted at the 3' end of the gene. Insertion of the 3.4 kb gB1 gene into plasmid pFS2.2 was demonstrated by Southern hybridization. E. coli K-12 strain JM-83 and Salmonella enteriditis serotype dublin strain SL1438 were each transformed with plasmid pAC61, screened for ampicillin resistance and for the production of an LT-B/gB1 fusion polypeptide by ELISA. Cytoplasmic protein fractions from these transformants bound to the LT-B receptor (GM1) and reacted with both anti-LT-B and anti- HSV -1 antisera. HSV -1 gB1 may have potential as an effective subunit vaccine. (0 ref)

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